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(54) Title: NOVEL PURIFIED POLYPEPTIDES FROM ENTEROCOCCUS FAECALIS

(57) Abstract: The present invention relates to novel drug targets for pathogenic bacteria. Accordingly, the invention provides purified protein comprising the amino acid sequence set forth in SEQ ID NO: 4. The invention also provides biochemical and biophysical characteristics of the polypeptides of the invention.

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NOVEL PURIFIED POLYPEPTIDES FROM ENTEROCOCCUS FAECALIS

RELATED APPLICATION INFORMATION

This application claims the benefit of priority to the following U.S. Provisional Patent Applications, all of which applications are hereby incorporated by reference in their entirety.

Provisional Application Number	*Filing Date*
U.S.S.N. 60/400,435	August 1, 2002
U.S.S.N. 60/453,405	March 10, 2003

INTRODUCTION

The discovery of novel antimicrobial agents that work by novel mechanisms is a problem researchers in all fields of drug development face today. The increasing prevalence of drug-resistant pathogens (bacteria, fungi, parasites, etc.) has led to significantly higher mortality rates from infectious diseases and currently presents a serious crisis worldwide. Despite the introduction of second and third generation antimicrobial drugs, certain pathogens have developed resistance to all currently available drugs.

One of the problems contributing to the development of multiple drug resistant pathogens is the limited number of protein targets for antimicrobial drugs. Many of the antibiotics currently in use are structurally related or act through common targets or pathways. Accordingly, adaptive mutation of a single gene may render a pathogenic species resistant to multiple classes of antimicrobial drugs. Therefore, the rapid discovery of drug targets is urgently needed in order to combat the constantly evolving threat by such infectious microorganisms.

Recent advances in bacterial and viral genomics research provides an opportunity for rapid progress in the identification of drug targets. The complete genomic sequences for a number of microorganisms are available. However, knowledge of the complete genomic sequence is only the first step in a long process toward discovery of a viable drug target. The genomic sequence must be annotated to identify open reading frames (ORFs), the essentiality of the protein encoded by the ORF must be determined and the mechanism of action of the gene product must be determined in order to develop a targeted approach to drug discovery.

There are a variety of computer programs available to annotate genomic sequences. Genome annotation involves both identification of genes as well assignment of function

thereto based on sequence comparison to homologous proteins with known or predicted functions. However, genome annotation has turned out to be much more of an art than a science. Factors such as splice variants and sequencing errors coupled with the particular algorithms and databases used to annotate the genome can result in significantly different annotations for the same genome. For example, upon reanalysis of the genome of *Mycoplasma pneumoniae* using more rigorous sequence comparisons coupled with molecular biological techniques, such as gel electrophoresis and mass spectrometry, researchers were able to identify several previously unidentified coding sequences, to dismiss a previous identified coding sequence as a likely pseudogene, and to adjust the length of several previously defined ORFs (Dandkar et al. (2000) Nucl. Acids Res. 28(17): 3278-3288). Furthermore, while overall conservation between amino acid sequences generally indicates a conservation of structure and function, specific changes at key residues can lead to significant variation in the biochemical and biophysical properties of a protein. In a comparison of three different functional annotations of the *Mycoplasma genitalium* genome, it was discovered that some genes were assigned three different functions and it was estimated that the overall error rate in the annotations was at least 8% (Brenner (1999) Trends Genet 15(4): 132-3). Accordingly, molecular biological techniques are required to ensure proper genome annotation and identify valid drug targets.

However, confirmation of genome annotation using molecular biological techniques is not an easy proposition due to the unpredictability in expression and purification of polypeptide sequences. Further, in order to carry out structural studies to validate proteins as potential drug targets, it is generally necessary to modify the native proteins in order to facilitate these analyses, e.g., by labeling the protein (e.g., with a heavy atom, isotopic label, polypeptide tag, etc.) or by creating fragments of the polypeptide corresponding to functional domains of a multi-domain protein. Moreover, it is well-known that even small changes in the amino acid sequence of a protein may lead to dramatic affects on protein solubility (Eberstadt et al. (1998) Nature 392: 941-945). Accordingly, genome-wide validation of protein targets will require considerable effort even in light of the sequence of the entire genome of an organism and/or purification conditions for homologs of a particular target.

We have developed reliable, high throughput methods to address some of the shortcomings identified above. In part, using these methods, we have now identified, expressed, and purified a novel antimicrobial target from *Enterococcus faecalis*, or *E.*

faecalis. Various biophysical, bioinformatic and biochemical studies have been used to characterize the structure and function of the polypeptides of the invention.

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SUMMARY OF THE INVENTION

As part of an effort at genome-wide structural and functional characterization of microbial targets, the present invention provides polypeptides from *E. faecalis*. In various aspects, the invention provides the nucleic acid and amino acid sequences of the polypeptides of the invention. The invention also provides purified, soluble forms of the polypeptides of the invention suitable for structural and functional characterization using a variety of techniques, including, for example, affinity chromatography, mass spectrometry, NMR and x-ray crystallography. The invention further provides modified versions of the polypeptides of the invention to facilitate characterization, including polypeptides labeled with isotopic or heavy atoms and fusion proteins.

A polypeptide of the invention has been crystallized and its structure solved as described in detail below, thereby providing information about the structure of the polypeptide, and druggable regions, domains and the like contained therein, all of which may be used in rational-based drug design efforts.

In general, the biological activity of a polypeptide of the invention is expected to be characterized as having a biochemical activity substantially similar to that of histidine tRNA synthetase, having the gene designation of *hisS*, as described in more detail below.

This assignment has been confirmed by solving the X-ray structure of a polypeptide of the invention.

All of the information learned and described herein about the polypeptides of the invention may be used to design modulators of one or more of their biological activities. In particular, information critical to the design of therapeutic and diagnostic molecules, including, for example, the protein domain, druggable regions, structural information, and the like for the polypeptides of the invention is now available or attainable as a result of the ability to prepare, purify and characterize them, and domains, fragments, variants and derivatives thereof.

In other aspects of the invention, structural and functional information about the polypeptides of the invention has and will be obtained. Such information, for example, may be incorporated into databases containing information on the polypeptides of the invention, as well as other polypeptide targets from other microbial species. Such databases will provide investigators with a powerful tool to analyze the polypeptides of the invention and aid in the rapid discovery and design of therapeutic and diagnostic molecules.

In another aspect, modulators, inhibitors, agonists or antagonists against the polypeptides of the invention, or biological complexes containing them, or orthologues thereto, may be used to treat any disease or other treatable condition of a patient (including humans and animals), and particularly a disease caused by *E. faecalis*, such as, for example, one of the following: urinary tract infection, surgical wound infection, bacteremia, intra abdominal infection, pelvic infection, central nervous system infection, osteomyelitis, pulmonary infection, and endocarditis.

The present invention further allows relationships between polypeptides from the same and multiple species to be compared by isolating and studying the various polypeptides of the invention and other proteins. By such comparison studies, which may involve multi-variable analysis as appropriate, it is possible to identify drugs that will affect multiple species or drugs that will affect one or a few species. In such a manner, so-called "wide spectrum" and narrow spectrum" anti-infectives may be identified. Alternatively, drugs that are selective for one or more bacterial or other non-mammalian species, and not for one or more mammalian species (especially human), may be identified (and vice-versa).

In other embodiments, the invention contemplates kits including the subject nucleic acids, polypeptides, crystallized polypeptides, antibodies, and other subject materials, and

optionally instructions for their use. Uses for such kits include, for example, diagnostic and therapeutic applications.

The embodiments and practices of the present invention, other embodiments, and their features and characteristics, will be apparent from the description, figures and claims that follow, with all of the claims hereby being incorporated by this reference into this Summary.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1 shows the nucleic acid coding sequence for an exemplary polypeptide of the invention as predicted from the genomic sequence of *E. faecalis* (SEQ ID NO: 1). This predicted nucleic acid coding sequence was cloned and sequenced to produce the polynucleotide sequence shown in FIGURE 2 (SEQ ID NO: 3).

FIGURE 2 shows the amino acid sequence for an exemplary polypeptide of the invention as predicted from the nucleotide sequence shown in FIGURE 1 (SEQ ID NO: 2).

FIGURE 3 shows the experimentally determined nucleic acid coding sequence for an exemplary polypeptide of the invention (SEQ ID NO: 3).

FIGURE 4 shows the amino acid sequence for the exemplary polypeptide of the invention as predicted from the nucleotide sequence shown in FIGURE 3 (SEQ ID NO: 4).

FIGURE 5 shows the primer sequences used to amplify the nucleic acid of SEQ ID NO: 3. The primers are SEQ ID NO: 5 and SEQ ID NO: 6.

FIGURE 6 contains Table 1, which provides among other things a variety of data and other information on the polypeptides of the invention.

FIGURE 7 contains Table 2, which provides the results of several bioinformatic analyses relating to SEQ ID NO: 2.

FIGURE 8 depicts the results of tryptic peptide mass spectrum peak searching as described in EXAMPLE 9.

FIGURE 9 depicts a MALDI-TOF mass spectrum of an intact polypeptide of the invention as described in EXAMPLE 10.

FIGURE 10 contains Table 3, which shows information related to the x-ray structure for a polypeptide of the invention as described more fully in EXAMPLE 16.

FIGURE 11 lists the atomic structure coordinates for a polypeptide of the invention derived from x-ray diffraction from a crystal of such polypeptide, as described in more detail in EXAMPLE 16. There are multiple pages to FIGURE 11, labeled 1, 2, 3, etc. The information in such Figure is presented in the following tabular format, with a generic entry provided as an example:

Record Header	No.	Atom Type	Resi -due	Residue Number	X	Y	Z	OCC	B
ATOM 1	1	CB	HIS	1	4.497	15.607	34.172	1	70.54

In the table, "Record Header" describes the row type, such as "ATOM". "No." refers to the row number. The first "Atom Type" column refers to the atom whose coordinates are measured, with the first letter in the column identifying the atom by its elemental symbol and the subsequent letter defining the location of the atom in the amino acid residue or other molecule. "Residue" and "residue number" identifies the residue of the subject polypeptide. "X, Y, Z" crystallographically define the atomic position of the atom measured. "Occ" is an occupancy factor that refers to the fraction of the molecules in which each atom occupies the position specified by the coordinates. A value of "1" indicates that each atom has the same conformation, i.e., the same position, in all molecules of the crystal. "B" is a thermal factor that is related to the root mean square deviation in the position of the atom around the given atomic coordinate.

FIGURE 12 depicts an alignment of the inferred amino acid sequence of *HisS* from six selected bacterial pathogens. Abbreviations: PA - *Pseudomonas aeruginosa*, EC - *Escherichia coli*, SA - *Staphylococcus aureus*, SP *Streptococcus pneumonia*, HP - *Heliobacter pylori* and EF *Enterococcus faecalis*.

FIGURE 13 depicts various views of the structure of the *E. faecalis HisS* molecule. FIGURE 13A depicts a ribbon diagram of the dimer of *HisS*, monomer A is colored blue, monomer (B) is colored red. FIGURE 13B depicts a ribbon diagram of the monomer of *HisS*. The N-terminal catalytic domain (Met1-Asp168, Leu227-Glu319) is colored green, the C-terminal domain (Leu330-Lys420) is colored yellow, the helical insertion domain (Met169-Phe226) is colored magenta and the small interface (SI) motif (Phe43-Leu77) is colored light blue. The histidine residues, likely from the cleaved histidine tag, are shown as blue sticks. All figures were produced in Pymol (Warren Delano Scientific) unless otherwise noted.

FIGURE 14 depicts an overlay of the *E. faecalis HisS* monomer (blue) and the *T. thermophilus HisS* monomer with histidine bound (PDB ID 1ADJ, in green).

FIGURE 15 depicts the predicted binding sites of *HisS*. FIGURE 15A depicts a ribbon diagram of the histidine binding site with the shape of the binding pocket shown as a mesh, with hydrophobic areas colored pink and hydrophilic area colored green. FIGURE 15B depicts a closer view of the protein showing the binding site for histidine with the binding site residues noted. Carbon atoms are light gray, oxygen, nitrogen and sulfur atoms are a darker shade of gray. FIGURE 15C depicts residues surrounding the binding pocket of histidine and the histidine found in the structure of *E. faecalis HisS*. FIGURE 15D depicts a comparison of the residues binding histidine in the *T. thermophilus HisS* structure (PDB ID:1ADJ) and *E. faecalis HisS*. The side chains of the *T. thermophilus* structure are green, except the histidines, which are yellow, and the *E. faecalis* structure is in gray. The overlay is based on a Cα overlay (r.m.s.d. 1.39) so the overlay of the side chains in the binding pocket is slightly distorted.

FIGURE 16 depicts various views of the conservation of the *HisS* amino acid sequence mapped onto the *E. faecalis HisS* protein structure. The *HisS* amino acid sequence from six pathogenic bacteria species - the *P. aeruginosa, E. coli, S. aureus, S. pneumonia, H. pylori* and *E. faecalis* - were aligned in ClustalX and the conservation of each position was evaluated in Consurf. The sequence conservation metric was then projected onto the *E. faecalis HisS* protein structure, with the convention that red residues are invariant, pink residues are somewhat variable but generally well conserved (with the degree of pinkness correlating with the degree of conservation), white residues show an average degree of conservation for that set, and blue residues are hyper-variable. FIGURE 16A depicts the conservation mapped onto a solvent accessible surface view of the dimer structure. FIGURE 16B depicts the conservation mapped onto a ribbon diagram of the monomer and the histidine binding residues.

DETAILED DESCRIPTION OF THE INVENTION

1. Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are collected here. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "amino acid" is intended to embrace all molecules, whether natural or synthetic, which include both an amino functionality and an acid functionality and capable of being included in a polymer of naturally-occurring amino acids. Exemplary amino acids include naturally-occurring amino acids; analogs, derivatives and congeners thereof; amino acid analogs having variant side chains; and all stereoisomers of any of any of the foregoing.

The term "binding" refers to an association, which may be a stable association, between two molecules, e.g., between a polypeptide of the invention and a binding partner, due to, for example, electrostatic, hydrophobic, ionic and/or hydrogen-bond interactions under physiological conditions.

A "comparison window," as used herein, refers to a conceptual segment of at least 20 contiguous amino acid positions wherein a protein sequence may be compared to a reference sequence of at least 20 contiguous amino acids and wherein the portion of the protein sequence in the comparison window may comprise additions or deletions (i.e., gaps) of 20 percent or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may be conducted by the local homology algorithm of Smith and Waterman (1981) Adv. Appl. Math. 2: 482, by the homology alignment algorithm of Needleman and Wunsch (1970) J. Mol. Biol. 48: 443, by the search for similarity method of Pearson and Lipman (1988) Proc. Natl. Acad. Sci. (U.S.A.) 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Dr., Madison, WI), or by inspection, and the best alignment (i.e., resulting in the highest percentage of homology over the comparison window) generated by the various methods may be identified.

The term "complex" refers to an association between at least two moieties (e.g. chemical or biochemical) that have an affinity for one another. Examples of complexes include associations between antigen/antibodies, lectin/avidin, target polynucleotide/probe oligonucleotide, antibody/anti-antibody, receptor/ligand, enzyme/ligand, polypeptide/ polypeptide, polypeptide/polynucleotide, polypeptide/co-factor, polypeptide/substrate,

polypeptide/inhibitor, polypeptide/small molecule, and the like. "Member of a complex" refers to one moiety of the complex, such as an antigen or ligand. "Protein complex" or "polypeptide complex" refers to a complex comprising at least one polypeptide.

The term "conserved residue" refers to an amino acid that is a member of a group of amino acids having certain common properties. The term "conservative amino acid substitution" refers to the substitution (conceptually or otherwise) of an amino acid from one such group with a different amino acid from the same group. A functional way to define common properties between individual amino acids is to analyze the normalized frequencies of amino acid changes between corresponding proteins of homologous organisms (Schulz, G. E. and R. H. Schirmer., Principles of Protein Structure, Springer-Verlag). According to such analyses, groups of amino acids may be defined where amino acids within a group exchange preferentially with each other, and therefore resemble each other most in their impact on the overall protein structure (Schulz, G. E. and R. H. Schirmer, Principles of Protein Structure, Springer-Verlag). One example of a set of amino acid groups defined in this manner include: (i) a charged group, consisting of Glu and Asp, Lys, Arg and His, (ii) a positively-charged group, consisting of Lys, Arg and His, (iii) a negatively-charged group, consisting of Glu and Asp, (iv) an aromatic group, consisting of Phe, Tyr and Trp, (v) a nitrogen ring group, consisting of His and Trp, (vi) a large aliphatic nonpolar group, consisting of Val, Leu and Ile, (vii) a slightly-polar group, consisting of Met and Cys, (viii) a small-residue group, consisting of Ser, Thr, Asp, Asn, Gly, Ala, Glu, Gln and Pro, (ix) an aliphatic group consisting of Val, Leu, Ile, Met and Cys, and (x) a small hydroxyl group consisting of Ser and Thr.

The term "domain", when used in connection with a polypeptide, refers to a specific region within such polypeptide that comprises a particular structure or mediates a particular function. In the typical case, a domain of a polypeptide of the invention is a fragment of the polypeptide. In certain instances, a domain is a structurally stable domain, as evidenced, for example, by mass spectroscopy, or by the fact that a modulator may bind to a druggable region of the domain.

The term "druggable region", when used in reference to a polypeptide, nucleic acid, complex and the like, refers to a region of the molecule which is a target or is a likely target for binding a modulator. For a polypeptide, a druggable region generally refers to a region wherein several amino acids of a polypeptide would be capable of interacting with a modulator or other molecule. For a polypeptide or complex thereof, exemplary druggable

regions including binding pockets and sites, enzymatic active sites, interfaces between domains of a polypeptide or complex, surface grooves or contours or surfaces of a polypeptide or complex which are capable of participating in interactions with another molecule. In certain instances, the interacting molecule is another polypeptide, which may be naturally-occurring. In other instances, the druggable region is on the surface of the molecule.

Druggable regions may be described and characterized in a number of ways. For example, a druggable region may be characterized by some or all of the amino acids that make up the region, or the backbone atoms thereof, or the side chain atoms thereof (optionally with or without the Cα atoms). Alternatively, in certain instances, the volume of a druggable region corresponds to that of a carbon based molecule of at least about 200 amu and often up to about 800 amu. In other instances, it will be appreciated that the volume of such region may correspond to a molecule of at least about 600 amu and often up to about 1600 amu or more.

Alternatively, a druggable region may be characterized by comparison to other regions on the same or other molecules. For example, the term "affinity region" refers to a druggable region on a molecule (such as a polypeptide of the invention) that is present in several other molecules, in so much as the structures of the same affinity regions are sufficiently the same so that they are expected to bind the same or related structural analogs. An example of an affinity region is an ATP-binding site of a protein kinase that is found in several protein kinases (whether or not of the same origin). The term "selectivity region" refers to a druggable region of a molecule that may not be found on other molecules, in so much as the structures of different selectivity regions are sufficiently different so that they are not expected to bind the same or related structural analogs. An exemplary selectivity region is a catalytic domain of a protein kinase that exhibits specificity for one substrate. In certain instances, a single modulator may bind to the same affinity region across a number of proteins that have a substantially similar biological function, whereas the same modulator may bind to only one selectivity region of one of those proteins.

Continuing with examples of different druggable regions, the term "undesired region" refers to a druggable region of a molecule that upon interacting with another molecule results in an undesirable affect. For example, a binding site that oxidizes the interacting molecule (such as P-450 activity) and thereby results in increased toxicity for

the oxidized molecule may be deemed a "undesired region". Other examples of potential undesired regions includes regions that upon interaction with a drug decrease the membrane permeability of the drug, increase the excretion of the drug, or increase the blood brain transport of the drug. It may be the case that, in certain circumstances, an undesired region will no longer be deemed an undesired region because the affect of the region will be favorable, e.g., a drug intended to treat a brain condition would benefit from interacting with a region that resulted in increased blood brain transport, whereas the same region could be deemed undesirable for drugs that were not intended to be delivered to the brain.

When used in reference to a druggable region, the "selectivity" or "specificity' of a molecule such as a modulator to a druggable region may be used to describe the binding between the molecule and a druggable region. For example, the selectivity of a modulator with respect to a druggable region may be expressed by comparison to another modulator, using the respective values of Kd (i.e., the dissociation constants for each modulator-druggable region complex) or, in cases where a biological effect is observed below the Kd, the ratio of the respective EC50's (i.e., the concentrations that produce 50% of the maximum response for the modulator interacting with each druggable region).

A "fusion protein" or "fusion polypeptide" refers to a chimeric protein as that term is known in the art and may be constructed using methods known in the art. In many examples of fusion proteins, there are two different polypeptide sequences, and in certain cases, there may be more. The sequences may be linked in frame. A fusion protein may include a domain which is found (albeit in a different protein) in an organism which also expresses the first protein, or it may be an "interspecies", "intergenic", etc. fusion expressed by different kinds of organisms. In various embodiments, the fusion polypeptide may comprise one or more amino acid sequences linked to a first polypeptide. In the case where more than one amino acid sequence is fused to a first polypeptide, the fusion sequences may be multiple copies of the same sequence, or alternatively, may be different amino acid sequences. The fusion polypeptides may be fused to the N-terminus, the C-terminus, or the N- and C-terminus of the first polypeptide. Exemplary fusion proteins include polypeptides comprising a glutathione S-transferase tag (GST-tag), histidine tag (His-tag), an immunoglobulin domain or an immunoglobulin binding domain.

The term "gene" refers to a nucleic acid comprising an open reading frame encoding a polypeptide having exon sequences and optionally intron sequences. The term "intron"

refers to a DNA sequence present in a given gene which is not translated into protein and is generally found between exons.

The term "having substantially similar biological activity", when used in reference to two polypeptides, refers to a biological activity of a first polypeptide which is substantially similar to at least one of the biological activities of a second polypeptide. A substantially similar biological activity means that the polypeptides carry out a similar function, e.g., a similar enzymatic reaction or a similar physiological process, etc. For example, two homologous proteins may have a substantially similar biological activity if they are involved in a similar enzymatic reaction, e.g., they are both kinases which catalyze phosphorylation of a substrate polypeptide, however, they may phosphorylate different regions on the same protein substrate or different substrate proteins altogether. Alternatively, two homologous proteins may also have a substantially similar biological activity if they are both involved in a similar physiological process, e.g., transcription. For example, two proteins may be transcription factors, however, they may bind to different DNA sequences or bind to different polypeptide interactors. Substantially similar biological activities may also be associated with proteins carrying out a similar structural role, for example, two membrane proteins.

The term "isolated polypeptide" refers to a polypeptide, in certain embodiments prepared from recombinant DNA or RNA, or of synthetic origin, or some combination thereof, which (1) is not associated with proteins that it is normally found with in nature, (2) is isolated from the cell in which it normally occurs, (3) is isolated free of other proteins from the same cellular source, e.g. free of other *E. faecalis* proteins, (4) is expressed by a cell from a different species, or (5) does not occur in nature.

The term "isolated nucleic acid" refers to a polynucleotide of genomic, cDNA, or synthetic origin or some combination there of, which (1) is not associated with the cell in which the "isolated nucleic acid" is found in nature, or (2) is operably linked to a polynucleotide to which it is not linked in nature.

The terms "label" or "labeled" refer to incorporation or attachment, optionally covalently or non-covalently, of a detectable marker into a molecule, such as a polypeptide. Various methods of labeling polypeptides are known in the art and may be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes, fluorescent labels, heavy atoms, enzymatic labels or reporter genes, chemiluminescent groups, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary

reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). Examples and use of such labels are described in more detail below. In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

The term "mammal" is known in the art, and exemplary mammals include humans, primates, bovines, porcines, canines, felines, and rodents (e.g., mice and rats).

The term "modulation", when used in reference to a functional property or biological activity or process (e.g., enzyme activity or receptor binding), refers to the capacity to either up regulate (e.g., activate or stimulate), down regulate (e.g., inhibit or suppress) or otherwise change a quality of such property, activity or process. In certain instances, such regulation may be contingent on the occurrence of a specific event, such as activation of a signal transduction pathway, and/or may be manifest only in particular cell types.

The term "modulator" refers to a polypeptide, nucleic acid, macromolecule, complex, molecule, small molecule, compound, species or the like (naturally-occurring or non-naturally-occurring), or an extract made from biological materials such as bacteria, plants, fungi, or animal cells or tissues, that may be capable of causing modulation. Modulators may be evaluated for potential activity as inhibitors or activators (directly or indirectly) of a functional property, biological activity or process, or combination of them, (e.g., agonist, partial antagonist, partial agonist, inverse agonist, antagonist, anti-microbial agents, inhibitors of microbial infection or proliferation, and the like) by inclusion in assays. In such assays, many modulators may be screened at one time. The activity of a modulator may be known, unknown or partially known.

The term "motif" refers to an amino acid sequence that is commonly found in a protein of a particular structure or function. Typically, a consensus sequence is defined to represent a particular motif. The consensus sequence need not be strictly defined and may contain positions of variability, degeneracy, variability of length, etc. The consensus sequence may be used to search a database to identify other proteins that may have a similar structure or function due to the presence of the motif in its amino acid sequence. For example, on-line databases may be searched with a consensus sequence in order to identify other proteins containing a particular motif. Various search algorithms and/or programs may be used, including FASTA, BLAST or ENTREZ. FASTA and BLAST are available as a part of the GCG sequence analysis package (University of Wisconsin, Madison, Wis.).

ENTREZ is available through the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, MD.

The term "naturally-occurring", as applied to an object, refers to the fact that an object may be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including bacteria) that may be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally-occurring.

The term "nucleic acid" refers to a polymeric form of nucleotides, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide. The terms should also be understood to include, as equivalents, analogs of either RNA or DNA made from nucleotide analogs, and, as applicable to the embodiment being described, single-stranded (such as sense or antisense) and double-stranded polynucleotides.

The term "nucleic acid of the invention" refers to a nucleic acid encoding a polypeptide of the invention, e.g., a nucleic acid comprising a sequence consisting of, or consisting essentially of, the polynucleotide sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 3. A nucleic acid of the invention may comprise all, or a portion of: the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3; a nucleotide sequence at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 1 or SEQ ID NO: 3; a nucleotide sequence that hybridizes under stringent conditions to SEQ ID NO: 1 or SEQ ID NO: 3; nucleotide sequences encoding polypeptides that are functionally equivalent to polypeptides of the invention; nucleotide sequences encoding polypeptides at least about 60%, 70%, 80%, 85%, 90%, 95%, 98%, 99% homologous or identical with an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4; nucleotide sequences encoding polypeptides having an activity of a polypeptide of the invention and having at least about 60%, 70%, 80%, 85%, 90%, 95%, 98%, 99% or more homology or identity with SEQ ID NO: 2 or SEQ ID NO: 4; nucleotide sequences that differ by 1 to about 2, 3, 5, 7, 10, 15, 20, 30, 50, 75 or more nucleotide substitutions, additions or deletions, such as allelic variants, of SEQ ID NO: 1 and SEQ ID NO: 3; nucleic acids derived from and evolutionarily related to SEQ ID NO: 1 or SEQ ID NO: 3; and complements of, and nucleotide sequences resulting from the degeneracy of the genetic code, for all of the foregoing and other nucleic acids of the invention. Nucleic acids of the invention also include homologs, e.g., orthologs and paralogs, of SEQ ID NO: 1 or SEQ ID NO: 3 and also variants of SEQ ID NO: 1 or SEQ ID

NO: 3 which have been codon optimized for expression in a particular organism (e.g., host cell).

The term "operably linked", when describing the relationship between two nucleic acid regions, refers to a juxtaposition wherein the regions are in a relationship permitting them to function in their intended manner. For example, a control sequence "operably linked" to a coding sequence is ligated in such a way that expression of the coding sequence is achieved under conditions compatible with the control sequences, such as when the appropriate molecules (e.g., inducers and polymerases) are bound to the control or regulatory sequence(s).

The term "phenotype" refers to the entire physical, biochemical, and physiological makeup of a cell, e.g., having any one trait or any group of traits.

The term "polypeptide", and the terms "protein" and "peptide" which are used interchangeably herein, refers to a polymer of amino acids. Exemplary polypeptides include gene products, naturally-occurring proteins, homologs, orthologs, paralogs, fragments, and other equivalents, variants and analogs of the foregoing.

The terms "polypeptide fragment" or "fragment", when used in reference to a reference polypeptide, refers to a polypeptide in which amino acid residues are deleted as compared to the reference polypeptide itself, but where the remaining amino acid sequence is usually identical to the corresponding positions in the reference polypeptide. Such deletions may occur at the amino-terminus or carboxy-terminus of the reference polypeptide, or alternatively both. Fragments typically are at least 5, 6, 8 or 10 amino acids long, at least 14 amino acids long, at least 20, 30, 40 or 50 amino acids long, at least 75 amino acids long, or at least 100, 150, 200, 300, 500 or more amino acids long. A fragment can retain one or more of the biological activities of the reference polypeptide. In certain embodiments, a fragment may comprise a druggable region, and optionally additional amino acids on one or both sides of the druggable region, which additional amino acids may number from 5, 10, 15, 20, 30, 40, 50, or up to 100 or more residues. Further, fragments can include a sub-fragment of a specific region, which sub-fragment retains a function of the region from which it is derived. In another embodiment, a fragment may have immunogenic properties.

The term "polypeptide of the invention" refers to a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4, or an equivalent or

fragment thereof, e.g., a polypeptide comprising a sequence consisting of, or consisting essentially of, the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4. Polypeptides of the invention include polypeptides comprising all or a portion of the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4 with 1 to about 2, 3, 5, 7, 10, 15, 20, 30, 50, 75 or more conservative amino acid substitutions; an amino acid sequence that is at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 2 or SEQ ID NO: 4; and functional fragments thereof. Polypeptides of the invention also include homologs, e.g., orthologs and paralogs, of SEQ ID NO: 2 or SEQ ID NO: 4.

The term "purified" refers to an object species that is the predominant species present (i.e., on a molar basis it is more abundant than any other individual species in the composition). A "purified fraction" is a composition wherein the object species comprises at least about 50 percent (on a molar basis) of all species present. In making the determination of the purity of a species in solution or dispersion, the solvent or matrix in which the species is dissolved or dispersed is usually not included in such determination; instead, only the species (including the one of interest) dissolved or dispersed are taken into account. Generally, a purified composition will have one species that comprises more than about 80 percent of all species present in the composition, more than about 85%, 90%, 95%, 99% or more of all species present. The object species may be purified to essential homogeneity (contaminant species cannot be detected in the composition by conventional detection methods) wherein the composition consists essentially of a single species. A skilled artisan may purify a polypeptide of the invention using standard techniques for protein purification in light of the teachings herein. Purity of a polypeptide may be determined by a number of methods known to those of skill in the art, including for example, amino-terminal amino acid sequence analysis, gel electrophoresis, mass-spectrometry analysis and the methods described in the Exemplification section herein.

The terms "recombinant protein" or "recombinant polypeptide" refer to a polypeptide which is produced by recombinant DNA techniques. An example of such techniques includes the case when DNA encoding the expressed protein is inserted into a suitable expression vector which is in turn used to transform a host cell to produce the protein or polypeptide encoded by the DNA.

A "reference sequence" is a defined sequence used as a basis for a sequence comparison; a reference sequence may be a subset of a larger sequence, for example, as a segment of a full-length protein given in a sequence listing such as SEQ ID NO: 2 or SEQ ID NO: 4, or may comprise a complete protein sequence. Generally, a reference sequence is at least 200, 300 or 400 nucleotides in length, frequently at least 600 nucleotides in length, and often at least 800 nucleotides in length (or the protein equivalent if it is shorter or longer in length). Because two proteins may each (1) comprise a sequence (i.e., a portion of the complete protein sequence) that is similar between the two proteins, and (2) may further comprise a sequence that is divergent between the two proteins, sequence comparisons between two (or more) proteins are typically performed by comparing sequences of the two proteins over a "comparison window" to identify and compare local regions of sequence similarity.

The term "regulatory sequence" is a generic term used throughout the specification to refer to polynucleotide sequences, such as initiation signals, enhancers, regulators and promoters, that are necessary or desirable to affect the expression of coding and non-coding sequences to which they are operably linked. Exemplary regulatory sequences are described in Goeddel; *Gene Expression Technology*: *Methods in Enzymology*, Academic Press, San Diego, CA (1990), and include, for example, the early and late promoters of SV40, adenovirus or cytomegalovirus immediate early promoter, the lac system, the trp system, the TAC or TRC system, T7 promoter whose expression is directed by T7 RNA polymerase, the major operator and promoter regions of phage lambda, the control regions for fd coat protein, the promoter for 3-phosphoglycerate kinase or other glycolytic enzymes, the promoters of acid phosphatase, e.g., Pho5, the promoters of the yeast α-mating factors, the polyhedron promoter of the baculovirus system and other sequences known to control the expression of genes of prokaryotic or eukaryotic cells or their viruses, and various combinations thereof. The nature and use of such control sequences may differ depending upon the host organism. In prokaryotes, such regulatory sequences generally include promoter, ribosomal binding site, and transcription termination sequences. The term "regulatory sequence" is intended to include, at a minimum, components whose presence may influence expression, and may also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences. In certain embodiments, transcription of a polynucleotide sequence is under the control of a promoter sequence (or other regulatory sequence) which controls the expression of the

polynucleotide in a cell-type in which expression is intended. It will also be understood that the polynucleotide can be under the control of regulatory sequences which are the same or different from those sequences which control expression of the naturally-occurring form of the polynucleotide.

The term "reporter gene" refers to a nucleic acid comprising a nucleotide sequence encoding a protein that is readily detectable either by its presence or activity, including, but not limited to, luciferase, fluorescent protein (e.g., green fluorescent protein), chloramphenicol acetyl transferase, β-galactosidase, secreted placental alkaline phosphatase, β-lactamase, human growth hormone, and other secreted enzyme reporters. Generally, a reporter gene encodes a polypeptide not otherwise produced by the host cell, which is detectable by analysis of the cell(s), e.g., by the direct fluorometric, radioisotopic or spectrophotometric analysis of the cell(s) and preferably without the need to kill the cells for signal analysis. In certain instances, a reporter gene encodes an enzyme, which produces a change in fluorometric properties of the host cell, which is detectable by qualitative, quantitative or semiquantitative function or transcriptional activation. Exemplary enzymes include esterases, β-lactamase, phosphatases, peroxidases, proteases (tissue plasminogen activator or urokinase) and other enzymes whose function may be detected by appropriate chromogenic or fluorogenic substrates known to those skilled in the art or developed in the future.

The term "sequence homology" refers to the proportion of base matches between two nucleic acid sequences or the proportion of amino acid matches between two amino acid sequences. When sequence homology is expressed as a percentage, e.g., 50%, the percentage denotes the proportion of matches over the length of sequence from a desired sequence (e.g., SEQ. ID NO: 1) that is compared to some other sequence. Gaps (in either of the two sequences) are permitted to maximize matching; gap lengths of 15 bases or less are usually used, 6 bases or less are used more frequently, with 2 bases or less used even more frequently. The term "sequence identity" means that sequences are identical (i.e., on a nucleotide-by-nucleotide basis for nucleic acids or amino acid-by-amino acid basis for polypeptides) over a window of comparison. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over the comparison window, determining the number of positions at which the identical amino acids occurs in both sequences to yield the number of matched positions, dividing the number of matched

positions by the total number of positions in the comparison window, and multiplying the result by 100 to yield the percentage of sequence identity. Methods to calculate sequence identity are known to those of skill in the art and described in further detail below.

The term "small molecule" refers to a compound, which has a molecular weight of less than about 5 kD, less than about 2.5 kD, less than about 1.5 kD, or less than about 0.9 kD. Small molecules may be, for example, nucleic acids, peptides, polypeptides, peptide nucleic acids, peptidomimetics, carbohydrates, lipids or other organic (carbon containing) or inorganic molecules. Many pharmaceutical companies have extensive libraries of chemical and/or biological mixtures, often fungal, bacterial, or algal extracts, which can be screened with any of the assays of the invention. The term "small organic molecule" refers to a small molecule that is often identified as being an organic or medicinal compound, and does not include molecules that are exclusively nucleic acids, peptides or polypeptides.

The term "soluble" as used herein with reference to a polypeptide of the invention or other protein, means that upon expression in cell culture, at least some portion of the polypeptide or protein expressed remains in the cytoplasmic fraction of the cell and does not fractionate with the cellular debris upon lysis and centrifugation of the lysate. Solubility of a polypeptide may be increased by a variety of art recognized methods, including fusion to a heterologous amino acid sequence, deletion of amino acid residues, amino acid substitution (e.g., enriching the sequence with amino acid residues having hydrophilic side chains), and chemical modification (e.g., addition of hydrophilic groups). The solubility of polypeptides may be measured using a variety of art recognized techniques, including, dynamic light scattering to determine aggregation state, UV absorption, centrifugation to separate aggregated from non-aggregated material, and SDS gel electrophoresis (e.g., the amount of protein in the soluble fraction is compared to the amount of protein in the soluble and insoluble fractions combined). When expressed in a host cell, the polypeptides of the invention may be at least about 1%, 2%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more soluble, e.g., at least about 1%, 2%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of the total amount of protein expressed in the cell is found in the cytoplasmic fraction. In certain embodiments, a one liter culture of cells expressing a polypeptide of the invention will produce at least about 0.1, 0.2, 0.5, 1, 2, 5, 10, 20, 30, 40, 50 milligrams or more of soluble protein. In an exemplary embodiment, a polypeptide of the invention is at least about 10% soluble and will produce at least about 1 milligram of protein from a one liter cell culture.

The term "specifically hybridizes" refers to detectable and specific nucleic acid binding. Polynucleotides, oligonucleotides and nucleic acids of the invention selectively hybridize to nucleic acid strands under hybridization and wash conditions that minimize appreciable amounts of detectable binding to nonspecific nucleic acids. Stringent conditions may be used to achieve selective hybridization conditions as known in the art and discussed herein. Generally, the nucleic acid sequence homology between the polynucleotides, oligonucleotides, and nucleic acids of the invention and a nucleic acid sequence of interest will be at least 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 98%, 99%, or more. In certain instances, hybridization and washing conditions are performed under stringent conditions according to conventional hybridization procedures and as described further herein.

The terms "stringent conditions" or "stringent hybridization conditions" refer to conditions which promote specific hydribization between two complementary polynucleotide strands so as to form a duplex. Stringent conditions may be selected to be about 5°C lower than the thermal melting point (Tm) for a given polynucleotide duplex at a defined ionic strength and pH. The length of the complementary polynucleotide strands and their GC content will determine the Tm of the duplex, and thus the hybridization conditions necessary for obtaining a desired specificity of hybridization. The Tm is the temperature (under defined ionic strength and pH) at which 50% of the a polynucleotide sequence hybridizes to a perfectly matched complementary strand. In certain cases it may be desirable to increase the stringency of the hybridization conditions to be about equal to the Tm for a particular duplex.

A variety of techniques for estimating the Tm are available. Typically, G-C base pairs in a duplex are estimated to contribute about 3°C to the Tm, while A-T base pairs are estimated to contribute about 2°C, up to a theoretical maximum of about 80-100°C. However, more sophisticated models of Tm are available in which G-C stacking interactions, solvent effects, the desired assay temperature and the like are taken into account. For example, probes can be designed to have a dissociation temperature (Td) of approximately 60°C, using the formula: Td = (((((3 x #GC) + (2 x #AT)) x 37) - 562)/#bp) - 5; where #GC, #AT, and #bp are the number of guanine-cytosine base pairs, the number of adenine-thymine base pairs, and the number of total base pairs, respectively, involved in the formation of the duplex.

Hybridization may be carried out in 5xSSC, 4xSSC, 3xSSC, 2xSSC, 1xSSC or 0.2xSSC for at least about 1 hour, 2 hours, 5 hours, 12 hours, or 24 hours. The temperature of the hybridization may be increased to adjust the stringency of the reaction, for example, from about 25°C (room temperature), to about 45°C, 50°C, 55°C, 60°C, or 65°C. The hybridization reaction may also include another agent affecting the stringency, for example, hybridization conducted in the presence of 50% formamide increases the stringency of hybridization at a defined temperature.

The hybridization reaction may be followed by a single wash step, or two or more wash steps, which may be at the same or a different salinity and temperature. For example, the temperature of the wash may be increased to adjust the stringency from about 25°C (room temperature), to about 45°C, 50°C, 55°C, 60°C, 65°C, or higher. The wash step may be conducted in the presence of a detergent, e.g., 0.1 or 0.2% SDS. For example, hybridization may be followed by two wash steps at 65°C each for about 20 minutes in 2xSSC, 0.1% SDS, and optionally two additional wash steps at 65°C each for about 20 minutes in 0.2xSSC, 0.1%SDS.

Exemplary stringent hybridization conditions include overnight hybridization at 65°C in a solution comprising, or consisting of, 50% formamide, 10xDenhardt (0.2% Ficoll, 0.2% Polyvinylpyrrolidone, 0.2% bovine serum albumin) and 200 µg/ml of denatured carrier DNA, e.g., sheared salmon sperm DNA, followed by two wash steps at 65°C each for about 20 minutes in 2xSSC, 0.1% SDS, and two wash steps at 65°C each for about 20 minutes in 0.2xSSC, 0.1%SDS.

Hybridization may consist of hybridizing two nucleic acids in solution, or a nucleic acid in solution to a nucleic acid attached to a solid support, e.g., a filter. When one nucleic acid is on a solid support, a prehybridization step may be conducted prior to hybridization. Prehybridization may be carried out for at least about 1 hour, 3 hours or 10 hours in the same solution and at the same temperature as the hybridization solution (without the complementary polynucleotide strand).

Appropriate stringency conditions are known to those skilled in the art or may be determined experimentally by the skilled artisan. See, for example, Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-12.3.6; Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, N.Y; S. Agrawal (ed.) Methods in Molecular Biology, volume 20; Tijssen (1993) Laboratory Techniques in biochemistry and molecular biology-hybridization with nucleic acid probes, e.g., part I

chapter 2 "Overview of principles of hybridization and the strategy of nucleic acid probe assays", Elsevier, New York; and Tibanyenda, N. et al., Eur. J. Biochem. 139:19 (1984) and Ebel, S. et al., Biochem. 31:12083 (1992).

As applied to proteins, the term "substantial identity" means that two protein sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, typically share at least about 70 percent sequence identity, alternatively at least about 80, 85, 90, 95 percent sequence identity or more. In certain instances, residue positions that are not identical differ by conservative amino acid substitutions, which are described above.

The term "structural motif', when used in reference to a polypeptide, refers to a polypeptide that, although it may have different amino acid sequences, may result in a similar structure, wherein by structure is meant that the motif forms generally the same tertiary structure, or that certain amino acid residues within the motif, or alternatively their backbone or side chains (which may or may not include the Cα atoms of the side chains) are positioned in a like relationship with respect to one another in the motif.

The term "test compound" refers to a molecule to be tested by one or more screening method(s) as a putative modulator of a polypeptide of the invention or other biological entity or process. A test compound is usually not known to bind to a target of interest. The term "control test compound" refers to a compound known to bind to the target (e.g., a known agonist, antagonist, partial agonist or inverse agonist). The term "test compound" does not include a chemical added as a control condition that alters the function of the target to determine signal specificity in an assay. Such control chemicals or conditions include chemicals that 1) nonspecifically or substantially disrupt protein structure (e.g., denaturing agents (e.g., urea or guanidinium), chaotropic agents, sulfhydryl reagents (e.g., dithiothreitol and β-mercaptoethanol), and proteases), 2) generally inhibit cell metabolism (e.g., mitochondrial uncouplers) and 3) non-specifically disrupt electrostatic or hydrophobic interactions of a protein (e.g., high salt concentrations, or detergents at concentrations sufficient to non-specifically disrupt hydrophobic interactions). Further, the term "test compound" also does not include compounds known to be unsuitable for a therapeutic use for a particular indication due to toxicity of the subject. In certain embodiments, various predetermined concentrations of test compounds are used for screening such as 0.01 μM, 0.1 μM, 1.0 μM, and 10.0 μM. Examples of test compounds include, but are not limited to, peptides, nucleic acids, carbohydrates, and small molecules.

The term "novel test compound" refers to a test compound that is not in existence as of the filing date of this application. In certain assays using novel test compounds, the novel test compounds comprise at least about 50%, 75%, 85%, 90%, 95% or more of the test compounds used in the assay or in any particular trial of the assay.

The term "therapeutically effective amount" refers to that amount of a modulator, drug or other molecule which is sufficient to effect treatment when administered to a subject in need of such treatment. The therapeutically effective amount will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

The term "transfection" means the introduction of a nucleic acid, e.g., an expression vector, into a recipient cell, which in certain instances involves nucleic acid-mediated gene transfer. The term "transformation" refers to a process in which a cell's genotype is changed as a result of the cellular uptake of exogenous nucleic acid. For example, a transformed cell may express a recombinant form of a polypeptide of the invention or antisense expression may occur from the transferred gene so that the expression of a naturally-occurring form of the gene is disrupted.

The term "transgene" means a nucleic acid sequence, which is partly or entirely heterologous to a transgenic animal or cell into which it is introduced, or, is homologous to an endogenous gene of the transgenic animal or cell into which it is introduced, but which is designed to be inserted, or is inserted, into the animal's genome in such a way as to alter the genome of the cell into which it is inserted (e.g., it is inserted at a location which differs from that of the natural gene or its insertion results in a knockout). A transgene may include one or more regulatory sequences and any other nucleic acids, such as introns, that may be necessary for optimal expression.

The term "transgenic animal" refers to any animal, for example, a mouse, rat or other non-human mammal, a bird or an amphibian, in which one or more of the cells of the animal contain heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or *in vitro* fertilization, but rather is directed to the introduction of a recombinant DNA molecule. This molecule may be integrated within a chromosome, or

it may be extrachromosomally replicating DNA. In the typical transgenic animals described herein, the transgene causes cells to express a recombinant form of a protein. However, transgenic animals in which the recombinant gene is silent are also contemplated.

The term "vector" refers to a nucleic acid capable of transporting another nucleic acid to which it has been linked. One type of vector which may be used in accord with the invention is an episome, i.e., a nucleic acid capable of extra-chromosomal replication. Other vectors include those capable of autonomous replication and expression of nucleic acids to which they are linked. Vectors capable of directing the expression of genes to which they are operatively linked are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of "plasmids" which refer to circular double stranded DNA molecules which, in their vector form are not bound to the chromosome. In the present specification, "plasmid" and "vector" are used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors which serve equivalent functions and which become known in the art subsequently hereto.

Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention.

2. Polypeptides of the Invention

The present invention makes available in a variety of embodiments soluble, purified and/or isolated forms of the polypeptides of the invention. Milligram quantities of an exemplary polypeptide of the invention, SEQ ID NO: 4 (optionally with a tag, and optionally labeled), have been isolated in a highly purified form. The present invention provides for expressing and purifying polypeptides of the invention in quantities that equal or exceed the quantity of polypeptide(s) of the invention expressed and purified as provided in the Exemplification section below (or smaller amount(s) thereof, such as 25%, 33%, 50% or 75% of the amount(s) so expressed and/or purified).

In one aspect, the present invention contemplates an isolated polypeptide comprising (a) the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4, (b)

the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4 with 1 to about 20 conservative amino acid substitutions, deletions or additions, (c) an amino acid sequence that is at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 4 or (d) a functional fragment of a polypeptide having an amino acid sequence set forth in (a), (b) or (c). In another aspect, the present invention contemplates a composition comprising such an isolated polypeptide and less than about 10%, or alternatively 5%, or alternatively 1%, contaminating biological macromolecules or polypeptides.

It may be the case that the amino acid sequence of SEQ ID NO: 4 differs from that of SEQ ID NO: 2 by one or more amino acids. SEQ ID NO: 4 is determined from the experimentally determined nucleic acid sequence SED ID NO: 3, and SEQ ID NO: 2 is determined from SEQ ID NO: 1, which is obtained as described in EXAMPLE 1. In such a case, the present invention contemplates the specific amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4, and variants thereof, as well as any differences (if any) in the polypeptides of the invention based on those SEQ ID NOS and nucleic acid sequences encoding the same.

In certain embodiments, a polypeptide of the invention is a fusion protein containing a domain which increases its solubility and/or facilitates its purification, identification, detection, and/or structural characterization. Exemplary domains, include, for example, glutathione S-transferase (GST), protein A, protein G, calmodulin-binding peptide, thioredoxin, maltose binding protein, HA, myc, poly arginine, poly His, poly His-Asp or FLAG fusion proteins and tags. Additional exemplary domains include domains that alter protein localization *in vivo*, such as signal peptides, type III secretion system-targeting peptides, transcytosis domains, nuclear localization signals, etc. In various embodiments, a polypeptide of the invention may comprise one or more heterologous fusions. Polypeptides may contain multiple copies of the same fusion domain or may contain fusions to two or more different domains. The fusions may occur at the N-terminus of the polypeptide, at the C-terminus of the polypeptide, or at both the N- and C-terminus of the polypeptide. It is also within the scope of the invention to include linker sequences between a polypeptide of the invention and the fusion domain in order to facilitate construction of the fusion protein or to optimize protein expression or structural constraints of the fusion protein. In another embodiment, the polypeptide may be constructed so as to contain protease cleavage sites between the fusion polypeptide and polypeptide of the invention in order to remove the tag

after protein expression or thereafter. Examples of suitable endoproteases, include, for example, Factor Xa and TEV proteases.

In another embodiment, a polypeptide of the invention may be modified so that its rate of traversing the cellular membrane is increased. For example, the polypeptide may be fused to a second peptide which promotes "transcytosis," e.g., uptake of the peptide by cells. The peptide may be a portion of the HIV transactivator (TAT) protein, such as the fragment corresponding to residues 37-62 or 48-60 of TAT, portions which have been observed to be rapidly taken up by a cell *in vitro* (Green and Loewenstein, (1989) Cell 55:1179-1188). Alternatively, the internalizing peptide may be derived from the *Drosophila antennapedia* protein, or homologs thereof. The 60 amino acid long homeodomain of the homeo-protein antennapedia has been demonstrated to translocate through biological membranes and can facilitate the translocation of heterologous polypeptides to which it is coupled. Thus, polypeptides may be fused to a peptide consisting of about amino acids 42-58 of *Drosophila antennapedia* or shorter fragments for transcytosis (Derossi et al. (1996) J Biol Chem 271:18188-18193; Derossi et al. (1994) J Biol Chem 269:10444-10450; and Perez et al. (1992) J Cell Sci 102:717-722). The transcytosis polypeptide may also be a non-naturally-occurring membrane-translocating sequence (MTS), such as the peptide sequences disclosed in U.S. Patent No. 6,248,558.

In another embodiment, a polypeptide of the invention is labeled with an isotopic label to facilitate its detection and or structural characterization using nuclear magnetic resonance or another applicable technique. Exemplary isotopic labels include radioisotopic labels such as, for example, potassium-40 (^{40}K), carbon-14 (^{14}C), tritium (^{3}H), sulphur-35 (^{35}S), phosphorus-32 (^{32}P), technetium-99m (^{99m}Tc), thallium-201 (^{201}Tl), gallium-67 (^{67}Ga), indium-111 (^{111}In), iodine-123 (^{123}I), iodine-131 (^{131}I), yttrium-90 (^{90}Y), samarium-153 (^{153}Sm), rhenium-186 (^{186}Re), rhenium-188 (^{188}Re), dysprosium-165 (^{165}Dy) and holmium-166 (^{166}Ho). The isotopic label may also be an atom with non zero nuclear spin, including, for example, hydrogen-1 (^{1}H), hydrogen-2 (^{2}H), hydrogen-3 (^{3}H), phosphorous-31 (^{31}P), sodium-23 (^{23}Na), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), carbon-13 (^{13}C) and fluorine-19 (^{19}F). In certain embodiments, the polypeptide is uniformly labeled with an isotopic label, for example, wherein at least 50%, 70%, 80%, 90%, 95%, or 98% of the possible labels in the polypeptide are labeled, e.g., wherein at least 50%, 70%, 80%, 90%, 95%, or 98% of the nitrogen atoms in the polypeptide are ^{15}N, and/or wherein at least 50%, 70%, 80%, 90%, 95%, or 98% of the carbon atoms in the polypeptide are ^{13}C, and/or

wherein at least 50%, 70%, 80%, 90%, 95%, or 98% of the hydrogen atoms in the polypeptide are ^{2}H. In other embodiments, the isotopic label is located in one or more specific locations within the polypeptide, for example, the label may be specifically incorporated into one or more of the leucine residues of the polypeptide. The invention also encompasses the embodiment wherein a single polypeptide comprises two, three or more different isotopic labels, for example, the polypeptide comprises both ^{15}N and ^{13}C labeling.

In yet another embodiment, the polypeptides of the invention are labeled to facilitate structural characterization using x-ray crystallography or another applicable technique. Exemplary labels include heavy atom labels such as, for example, cobalt, selenium, krypton, bromine, strontium, molybdenum, ruthenium, rhodium, palladium, silver, cadmium, tin, iodine, xenon, barium, lanthanum, cerium, praseodymium, neodymium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium, lutetium, tantalum, tungsten, rhenium, osmium, iridium, platinum, gold, mercury, thallium, lead, thorium and uranium. In an exemplary embodiment, the polypeptide is labeled with seleno-methionine.

A variety of methods are available for preparing a polypeptide with a label, such as a radioisotopic label or heavy atom label. For example, in one such method, an expression vector comprising a nucleic acid encoding a polypeptide is introduced into a host cell, and the host cell is cultured in a cell culture medium in the presence of a source of the label, thereby generating a labeled polypeptide. As indicated above, the extent to which a polypeptide may be labeled may vary.

In still another embodiment, the polypeptides of the invention are labeled with a fluorescent label to facilitate their detection, purification, or structural characterization. In an exemplary embodiment, a polypeptide of the invention is fused to a heterologous polypeptide sequence which produces a detectable fluorescent signal, including, for example, green fluorescent protein (GFP), enhanced green fluorescent protein (EGFP), *Renilla Reniformis* green fluorescent protein, GFPmut2, GFPuv4, enhanced yellow fluorescent protein (EYFP), enhanced cyan fluorescent protein (ECFP), enhanced blue fluorescent protein (EBFP), citrine and red fluorescent protein from discosoma (dsRED).

In other embodiments, the invention provides for polypeptides of the invention immobilized onto a solid surface, including, microtiter plates, slides, beads, films, etc. The polypeptides of the invention may be immobilized onto a "chip" as part of an array. An array, having a plurality of addresses, may comprise one or more polypeptides of the

invention in one or more of those addresses. In one embodiment, the chip comprises one or more polypeptides of the invention as part of an array of *E. faecalis* polypeptide sequences.

In other embodiments, the invention provides for polypeptides of the invention immobilized onto a solid surface, including, plates, microtiter plates, slides, beads, particles, spheres, films, strands, precipitates, gels, sheets, tubing, containers, capillaries, pads, slices, etc. The polypeptides of the invention may be immobilized onto a "chip" as part of an array. An array, having a plurality of addresses, may comprise one or more polypeptides of the invention in one or more of those addresses. In one embodiment, the chip comprises one or more polypeptides of the invention as part of an array that contains at least some polypeptide sequences from *E. faecalis*.

In still other embodiments, the invention comprises the polypeptide sequences of the invention in computer readable format. The invention also encompasses a database comprising the polypeptide sequences of the invention.

In other embodiments, the invention relates to the polypeptides of the invention contained within a vessels useful for manipulation of the polypeptide sample. For example, the polypeptides of the invention may be contained within a microtiter plate to facilitate detection, screening or purification of the polypeptide. The polypeptides may also be contained within a syringe as a container suitable for administering the polypeptide to a subject in order to generate antibodies or as part of a vaccination regimen. The polypeptides may also be contained within an NMR tube in order to enable characterization by nuclear magnetic resonance techniques.

In still other embodiments, the invention relates to a crystallized polypeptide of the invention and crystallized polypeptides which have been mounted for examination by x-ray crystallography as described further below. In certain instances, a polypeptide of the invention in crystal form may be single crystals of various dimensions (e.g., micro-crystals) or may be an aggregate of crystalline material. In another aspect, the present invention contemplates a crystallized complex including a polypeptide of the invention and one or more of the following: a co-factor (such as a salt, metal, nucleotide, oligonucleotide or polypeptide), a modulator, or a small molecule. In another aspect, the present invention contemplates a crystallized complex including a polypeptide of the invention and any other molecule or atom (such as a metal ion) that associates with the polypeptide *in vivo*.

In certain embodiments, polypeptides of the invention may be synthesized chemically, ribosomally in a cell free system, or ribosomally within a cell. Chemical

synthesis of polypeptides of the invention may be carried out using a variety of art recognized methods, including stepwise solid phase synthesis, semi-synthesis through the conformationally-assisted re-ligation of peptide fragments, enzymatic ligation of cloned or synthetic peptide segments, and chemical ligation. Native chemical ligation employs a chemoselective reaction of two unprotected peptide segments to produce a transient thioester-linked intermediate. The transient thioester-linked intermediate then spontaneously undergoes a rearrangement to provide the full length ligation product having a native peptide bond at the ligation site. Full length ligation products are chemically identical to proteins produced by cell free synthesis. Full length ligation products may be refolded and/or oxidized, as allowed, to form native disulfide-containing protein molecules. (see e.g., U.S. Patent Nos. 6,184,344 and 6,174,530; and T. W. Muir et al., Curr. Opin. Biotech. (1993): vol. 4, p 420; M. Miller, et al., Science (1989): vol. 246, p 1149; A. Wlodawer, et al., Science (1989): vol. 245, p 616; L. H. Huang, et al., Biochemistry (1991): vol. 30, p 7402; M. Schnolzer, et al., Int. J. Pept. Prot. Res. (1992): vol. 40, p 180-193; K. Rajarathnam, et al., Science (1994): vol. 264, p 90; R. E. Offord, "Chemical Approaches to Protein Engineering", in Protein Design and the Development of New therapeutics and Vaccines, J. B. Hook, G. Poste, Eds., (Plenum Press, New York, 1990) pp. 253-282; C. J. A. Wallace, et al., J. Biol. Chem. (1992): vol. 267, p 3852; L. Abrahmsen, et al., Biochemistry (1991): vol. 30, p 4151; T. K. Chang, et al., Proc. Natl. Acad. Sci. USA (1994) 91: 12544-12548; M. Schnlzer, et al., Science (1992): vol., 3256, p 221; and K. Akaji, et al., Chem. Pharm. Bull. (Tokyo) (1985) 33: 184).

In certain embodiments, it may be advantageous to provide naturally-occurring or experimentally-derived homologs of a polypeptide of the invention. Such homologs may function in a limited capacity as a modulator to promote or inhibit a subset of the biological activities of the naturally-occurring form of the polypeptide. Thus, specific biological effects may be elicited by treatment with a homolog of limited function, and with fewer side effects relative to treatment with agonists or antagonists which are directed to all of the biological activities of a polypeptide of the invention. For instance, antagonistic homologs may be generated which interfere with the ability of the wild-type polypeptide of the invention to associate with certain proteins, but which do not substantially interfere with the formation of complexes between the native polypeptide and other cellular proteins.

Another aspect of the invention relates to polypeptides derived from the full-length polypeptides of the invention. Isolated peptidyl portions of those polypeptides may be

obtained by screening polypeptides recombinantly produced from the corresponding fragment of the nucleic acid encoding such polypeptides. In addition, fragments may be chemically synthesized using techniques known in the art such as conventional Merrifield solid phase f-Moc or t-Boc chemistry. For example, proteins may be arbitrarily divided into fragments of desired length with no overlap of the fragments, or may be divided into overlapping fragments of a desired length. The fragments may be produced (recombinantly or by chemical synthesis) and tested to identify those peptidyl fragments having a desired property, for example, the capability of functioning as a modulator of the polypeptides of the invention. In an illustrative embodiment, peptidyl portions of a protein of the invention may be tested for binding activity, as well as inhibitory ability, by expression as, for example, thioredoxin fusion proteins, each of which contains a discrete fragment of a protein of the invention (see, for example, U.S. Patents 5,270,181 and 5,292,646; and PCT publication WO94/ 02502).

In another embodiment, truncated polypeptides may be prepared. Truncated polypeptides have from 1 to 20 or more amino acid residues removed from either or both the N- and C-termini. Such truncated polypeptides may prove more amenable to expression, purification or characterization than the full-length polypeptide. For example, truncated polypeptides may prove more amenable than the full-length polypeptide to crystallization, to yielding high quality diffracting crystals or to yielding an HSQC spectrum with high intensity peaks and minimally overlapping peaks. In addition, the use of truncated polypeptides may also identify stable and active domains of the full-length polypeptide that may be more amenable to characterization.

It is also possible to modify the structure of the polypeptides of the invention for such purposes as enhancing therapeutic or prophylactic efficacy, or stability (e.g., *ex vivo* shelf life, resistance to proteolytic degradation *in vivo*, etc.). Such modified polypeptides, when designed to retain at least one activity of the naturally-occurring form of the protein, are considered "functional equivalents" of the polypeptides described in more detail herein. Such modified polypeptides may be produced, for instance, by amino acid substitution, deletion, or addition, which substitutions may consist in whole or part by conservative amino acid substitutions.

For instance, it is reasonable to expect that an isolated conservative amino acid substitution, such as replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, will not have a major affect on the biological activity

of the resulting molecule. Whether a change in the amino acid sequence of a polypeptide results in a functional homolog may be readily determined by assessing the ability of the variant polypeptide to produce a response similar to that of the wild-type protein. Polypeptides in which more than one replacement has taken place may readily be tested in the same manner.

This invention further contemplates a method of generating sets of combinatorial mutants of polypeptides of the invention, as well as truncation mutants, and is especially useful for identifying potential variant sequences (e.g. homologs). The purpose of screening such combinatorial libraries is to generate, for example, homologs which may modulate the activity of a polypeptide of the invention, or alternatively, which possess novel activities altogether. Combinatorially-derived homologs may be generated which have a selective potency relative to a naturally-occurring protein. Such homologs may be used in the development of therapeutics.

Likewise, mutagenesis may give rise to homologs which have intracellular half-lives dramatically different than the corresponding wild-type protein. For example, the altered protein may be rendered either more stable or less stable to proteolytic degradation or other cellular process which result in destruction of, or otherwise inactivation of the protein. Such homologs, and the genes which encode them, may be utilized to alter protein expression by modulating the half-life of the protein. As above, such proteins may be used for the development of therapeutics or treatment.

In similar fashion, protein homologs may be generated by the present combinatorial approach to act as antagonists, in that they are able to interfere with the activity of the corresponding wild-type protein.

In a representative embodiment of this method, the amino acid sequences for a population of protein homologs are aligned, preferably to promote the highest homology possible. Such a population of variants may include, for example, homologs from one or more species, or homologs from the same species but which differ due to mutation. Amino acids which appear at each position of the aligned sequences are selected to create a degenerate set of combinatorial sequences. In certain embodiments, the combinatorial library is produced by way of a degenerate library of genes encoding a library of polypeptides which each include at least a portion of potential protein sequences. For instance, a mixture of synthetic oligonucleotides may be enzymatically ligated into gene sequences such that the degenerate set of potential nucleotide sequences are expressible as

individual polypeptides, or alternatively, as a set of larger fusion proteins (e.g. for phage display).

There are many ways by which the library of potential homologs may be generated from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence may be carried out in an automatic DNA synthesizer, and the synthetic genes may then be ligated into an appropriate vector for expression. One purpose of a degenerate set of genes is to provide, in one mixture, all of the sequences encoding the desired set of potential protein sequences. The synthesis of degenerate oligonucleotides is well known in the art (see for example, Narang, SA (1983) *Tetrahedron* 39:3; Itakura et al., (1981) *Recombinant DNA, Proc.* 3rd Cleveland Sympos. Macromolecules, ed. AG Walton, Amsterdam: Elsevier pp. 273-289; Itakura et al., (1984) *Annu. Rev. Biochem.* 53:323; Itakura et al., (1984) *Science* 198:1056; Ike et al., (1983) *Nucleic Acid Res.* 11:477). Such techniques have been employed in the directed evolution of other proteins (see, for example, Scott et al., (1990) *Science* 249:386-390; Roberts et al., (1992) *PNAS USA* 89:2429-2433; Devlin et al., (1990) *Science* 249: 404-406; Cwirla et al., (1990) *PNAS USA* 87: 6378-6382; as well as U.S. Patent Nos: 5,223,409, 5,198,346, and 5,096,815).

Alternatively, other forms of mutagenesis may be utilized to generate a combinatorial library. For example, protein homologs (both agonist and antagonist forms) may be generated and isolated from a library by screening using, for example, alanine scanning mutagenesis and the like (Ruf et al., (1994) *Biochemistry* 33:1565-1572; Wang et al., (1994) *J. Biol. Chem.* 269:3095-3099; Balint et al., (1993) *Gene* 137:109-118; Grodberg et al., (1993) *Eur. J. Biochem.* 218:597-601; Nagashima et al., (1993) *J. Biol. Chem.* 268:2888-2892; Lowman et al., (1991) *Biochemistry* 30:10832-10838; and Cunningham et al., (1989) *Science* 244:1081-1085), by linker scanning mutagenesis (Gustin et al., (1993) *Virology* 193:653-660; Brown et al., (1992) *Mol. Cell Biol.* 12:2644-2652; McKnight et al., (1982) *Science* 232:316); by saturation mutagenesis (Meyers et al., (1986) *Science* 232:613); by PCR mutagenesis (Leung et al., (1989) *Method Cell Mol Biol* 1:11-19); or by random mutagenesis (Miller et al., (1992) A Short Course in Bacterial Genetics, CSHL Press, Cold Spring Harbor, NY; and Greener et al., (1994) *Strategies in Mol Biol* 7:32-34). Linker scanning mutagenesis, particularly in a combinatorial setting, is an attractive method for identifying truncated forms of proteins that are bioactive.

A wide range of techniques are known in the art for screening gene products of combinatorial libraries made by point mutations and truncations, and for screening cDNA

libraries for gene products having a certain property. Such techniques will be generally adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of protein homologs. The most widely used techniques for screening large gene libraries typically comprises cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates relatively easy isolation of the vector encoding the gene whose product was detected. Each of the illustrative assays described below are amenable to high throughput analysis as necessary to screen large numbers of degenerate sequences created by combinatorial mutagenesis techniques.

In an illustrative embodiment of a screening assay, candidate combinatorial gene products are displayed on the surface of a cell and the ability of particular cells or viral particles to bind to the combinatorial gene product is detected in a "panning assay". For instance, the gene library may be cloned into the gene for a surface membrane protein of a bacterial cell (Ladner et al., WO 88/06630; Fuchs et al., (1991) *Bio/Technology* 9:1370-1371; and Goward et al., (1992) *TIBS* 18:136-140), and the resulting fusion protein detected by panning, e.g. using a fluorescently labeled molecule which binds the cell surface protein, e.g. FITC-substrate, to score for potentially functional homologs. Cells may be visually inspected and separated under a fluorescence microscope, or, when the morphology of the cell permits, separated by a fluorescence-activated cell sorter. This method may be used to identify substrates or other polypeptides that can interact with a polypeptide of the invention.

In similar fashion, the gene library may be expressed as a fusion protein on the surface of a viral particle. For instance, in the filamentous phage system, foreign peptide sequences may be expressed on the surface of infectious phage, thereby conferring two benefits. First, because these phage may be applied to affinity matrices at very high concentrations, a large number of phage may be screened at one time. Second, because each infectious phage displays the combinatorial gene product on its surface, if a particular phage is recovered from an affinity matrix in low yield, the phage may be amplified by another round of infection. The group of almost identical *E. coli* filamentous phages M13, fd, and f1 are most often used in phage display libraries, as either of the phage gIII or gVIII coat proteins may be used to generate fusion proteins without disrupting the ultimate packaging of the viral particle (Ladner et al., PCT publication WO 90/02909; Garrard et al.,

PCT publication WO 92/09690; Marks et al., (1992) *J. Biol. Chem.* 267:16007-16010; Griffiths et al., (1993) *EMBO J.* 12:725-734; Clackson et al., (1991) *Nature* 352:624-628; and Barbas et al., (1992) *PNAS USA* 89:4457-4461). Other phage coat proteins may be used as appropriate.

The invention also provides for reduction of the polypeptides of the invention to generate mimetics, e.g. peptide or non-peptide agents, which are able to mimic binding of the authentic protein to another cellular partner. Such mutagenic techniques as described above, as well as the thioredoxin system, are also particularly useful for mapping the determinants of a protein which participates in a protein-protein interaction with another protein. To illustrate, the critical residues of a protein which are involved in molecular recognition of a substrate protein may be determined and used to generate peptidomimetics that may bind to the substrate protein. The peptidomimetic may then be used as an inhibitor of the wild-type protein by binding to the substrate and covering up the critical residues needed for interaction with the wild-type protein, thereby preventing interaction of the protein and the substrate. By employing, for example, scanning mutagenesis to map the amino acid residues of a protein which are involved in binding a substrate polypeptide, peptidomimetic compounds may be generated which mimic those residues in binding to the substrate. For instance, non-hydrolyzable peptide analogs of such residues may be generated using benzodiazepine (e.g., see Freidinger et al., in *Peptides: Chemistry and Biology*, G.R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), azepine (e.g., see Huffman et al., in *Peptides: Chemistry and Biology*, G.R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), substituted gamma lactam rings (Garvey et al., in *Peptides: Chemistry and Biology*, G.R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), keto-methylene pseudopeptides (Ewenson et al., (1986) *J. Med. Chem.* 29:295; and Ewenson et al., in *Peptides: Structure and Function* (Proceedings of the 9th American Peptide Symposium) Pierce Chemical Co. Rockland, IL, 1985), β-turn dipeptide cores (Nagai et al., (1985) *Tetrahedron Lett* 26:647; and Sato et al., (1986) *J Chem Soc Perkin Trans* 1:1231), and β-aminoalcohols (Gordon et al., (1985) *Biochem Biophys Res Commun* 126:419; and Dann et al., (1986) *Biochem Biophys Res Commun* 134:71).

The activity of a polypeptide of the invention may be identified and/or assayed using a variety of methods well known to the skilled artisan. For example, information about the activity of non-essential genes may be assayed by creating a null mutant strain of bacteria expressing a mutant form of, or lacking expression of, a protein of interest. The

resulting phenotype of the null mutant strain may provide information about the activity of the mutated gene product. Essential genes may be studied by creating a bacterial strain with a conditional mutation in the gene of interest. The bacterial strain may be grown under permissive and non-permissive conditions and the change in phenotype under the non-permissive conditions may be used to identify and/or assay the activity of the gene product.

In an alternative embodiment, the activity of a protein may be assayed using an appropriate substrate or binding partner or other reagent suitable to test for the suspected activity. For catalytic activity, the assay is typically designed so that the enzymatic reaction produces a detectable signal. For example, mixture of a kinase with a substrate in the presence of ^{32}P will result in incorporation of the ^{32}P into the substrate. The labeled substrate may then be separated from the free ^{32}P and the presence and/or amount of radiolabeled substrate may be detected using a scintillation counter or a phosphorimager. Similar assays may be designed to identify and/or assay the activity of a wide variety of enzymatic activities. Based on the teachings herein, the skilled artisan would readily be able to develop an appropriate assay for a polypeptide of the invention.

In another embodiment, the activity of a polypeptide of the invention may be determined by assaying for the level of expression of RNA and/or protein molecules. Transcription levels may be determined, for example, using Northern blots, hybridization to an oligonucleotide array or by assaying for the level of a resulting protein product. Translation levels may be determined, for example, using Western blotting or by identifying a detectable signal produced by a protein product (e.g., fluorescence, luminescence, enzymatic activity, etc.). Depending on the particular situation, it may be desirable to detect the level of transcription and/or translation of a single gene or of multiple genes.

Alternatively, it may be desirable to measure the overall rate of DNA replication, transcription and/or translation in a cell. In general this may be accomplished by growing the cell in the presence of a detectable metabolite which is incorporated into the resultant DNA, RNA, or protein product. For example, the rate of DNA synthesis may be determined by growing cells in the presence of BrdU which is incorporated into the newly synthesized DNA. The amount of BrdU may then be determined histochemically using an anti-BrdU antibody.

In general, the biological activity of a polypeptide encoded by SEQ ID NO. 2, and possibly other polypeptides of the invention, is expected to be characterized as having a biochemical activity substantially similar to that of histidine tRNA synthetase, having the gene designation of *hisS*, although the target specificity and/or other biological context for the biological activity of a polypeptide of the invention may be somewhat different from that protein. An alternate gene designation for histidine tRNA synthetase is *Syh*. The foregoing annotations were determined in accordance with the procedure described in EXAMPLE 17. This functionality asignment has been confirmed by completion of the X-ray structure of a polypeptide of the invention, as described in more detail below. In one aspect, the present invention contemplates a polypeptide having biological activity, or is a component of a protein complex having biological activity, substantially similar to or identical to histidine tRNA synthetase. Alternatively, the polypeptide catalyzes, or is a component of a protein complex that catalyzes, a reaction that is substantially the same type of, or is the same as, the reaction catalyzed by histidine tRNA synthetase. Other biological activities of polypeptides of the invention are described herein, or will be reasonably apparent to those skilled in the art in light of the present disclosure.

The enzymes involved in aminoacyl-tRNA (AA-tRNA) synthesis, a process substantially responsible for the accuracy of protein synthesis, are believed to be highly species-specific. In particular, a number of pathogens contain certain pathways of AA-tRNA synthesis that are unrelated to those found in their mammalian hosts. Since AA-tRNA synthesis is believed to be required for cell viability, the discovery of pathogen-specific pathways and enzymes, including the polypeptides of the present invention, presents novel therapeutic and diagnostic targets. Such enzymes are reported as being the targets of several known drugs. Some microorganisms, however, are resistance to such drugs, for example, some strains of *Streptococcus pneumoniae* have been reported as having varying resistance to the drug mupirocin.

Aminoacyl-tRNA synthetases (AARS) is thought to catalyze the first step in protein synthesis by the formation of aminoacyl adenylate (AA-AMP) and to transfer it onto tRNA to form charged tRNA to allow protein synthesis to proceed. In these reactions, an amino acid is associated with a specific nucleotide triplet of the genetic code by virtue of being linked to a specific tRNA that harbors the anticodon triplet cognate to the amino acid. Most organisms make twenty different aminoacyl-tRNA synthetases, one for each type of amino acid. These twenty enzymes are known to be widely different, each optimized for function

with its own particular amino acid and the set of tRNA molecules appropriate to that amino acid. It is necessary that aminoacyl-tRNA synthetases perform their tasks with high accuracy, for each mistake they make will result in a misplaced amino acid when new proteins are constructed. It has been observed that such enzymes make about one mistake in 10,000. Aminoacyl-tRNA synthetases are essential proteins found in all living organisms. They form a diverse group of enzymes that ensure the fidelity of transfer of genetic information from the DNA into the protein.

Histidyl-tRNA synthetase (HisRS or Syh), which has been observed to catalyze the charging of histidine onto its cognate tRNA His, is a homo-dimer of about 95 kDa. Histidine is one of the most critical amino acids in proteins, found often as a catalytic residue or a ligand for metals. A high degree of accuracy for charging tRNAHis with the correct amino acid is very important. HisRS is a class II aminoacyl-tRNA synthetase, and has been further grouped into subclass IIa, along with seryl-, prolyl-, threonyl-, and some glycyl-tRNA synthetases on the basis of sequence similarities in the C-terminal anticodon-binding domain. However, it is distinct from other class IIa synthetases in that HisRS has two additional motifs, histidine A (HisA, RGLDYY) and histidine B (HisB,GGRYDG), both of which are conserved among all known HisRS.

There are several postulated mechanisms for improving charging fidelity of the tRNA synthetases. One of them uses a preformed and well-defined amino acid binding pocket. For example, TyrRS has a pocket that appears to provide sufficient affinity differences to discriminate between tyrosine and the closely related phenylalanine and GlnRS appears to use additional elements from tRNA to establish the amino acid binding pocket. IleRS illustrates another mechanism, in which the rigid amino acid binding site is thought not to provide enough discrimination against valine. Therefore, a hydrolytic editing domain is thought to have evolved to correct these errors in IleRS. The dynamic HisA motif found when comparing the apo and holo structures in HisRS offers a third novel fidelity mechanism. Although substrate binding and catalysis require some degree of cooperative dynamics in other synthetases, the large-scale cooperative dynamics proposed for HisRS may have evolved for charging fidelity as well as efficient product release.

Histidine-specific tRNAs are thought to be unique due to the additional guanosine (designated G-1) present at their 5' end, giving rise through pairing with the discriminator base (C73 in prokaryotes and organelles, A73 or G73 in eukaryotes) to an extra base pair in the acceptor stem. From the results of *in vitro* transcript amino-acylation experiments, the

G-1,C73 base pair in *E. coli* is thought to be the most important determinant for HisRS. Furthermore, mini helices corresponding to the acceptor stem and loop of tRNAHis have been observed to be efficiently amino-acylated by HisRS. More recently, *in vivo* studies have indicated that the identity of histidine tRNAs in *E. coli* depends more on C73 than G-1. On the other hand, in the yeast histidyl system, the exact nature of the additional base pair seems less important (except that G73 is a strong negative determinant), suggesting that the major recognition elements may be the extra backbone groups at the 5' end. For specific recognition of the GUG anti-codon, *in vitro* results suggest that in the *E. coli* system the anticodon bases are weak identity elements, whereas in the yeast system bases 34 and 35, but not 36, are relatively more important. The manner of binding of the C-terminal domain of class IIa synthetases to the anticodon stem-loop is one of the remaining open structural questions about this subclass of synthetases.

For all of the foregoing reasons, the polypeptides of the present invention are potentially valuable targets for therapeutics and diagnostics.

3. Nucleic Acids of the Invention

One aspect of the invention pertains to isolated nucleic acids of the invention. For example, the present invention contemplates an isolated nucleic acid comprising (a) the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3, (b) a nucleotide sequence at least 80% identical to SEQ ID NO: 1 or SEQ ID NO: 3, (c) a nucleotide sequence that hybridizes under stringent conditions to SEQ ID NO: 1 or SEQ ID NO: 3, or (d) the complement of the nucleotide sequence of (a), (b) or (c). In certain embodiments, nucleic acids of the invention may be labeled, with for example, a radioactive, chemiluminescent or fluorescent label.

It may be that case that the nucleic acid sequence of SEQ ID NO: 3 differs from that of SEQ ID NO: 1 by one or more nucleic acid residues. SEQ ID NO: 3 is determined experimetally, and SEQ ID NO: 1 obtained as described in EXAMPLE 1. In such a case, the present invention contemplates the specific nucleic acid sequences of SEQ ID NO: 1 and SEQ ID NO: 3, and variants thereof, as well as any differences in the applicable amino acid sequences encoded thereby.

In another aspect, the present invention contemplates an isolated nucleic acid that specifically hybridizes under stringent conditions to at least ten nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3, or the complement thereof, which nucleic acid can specifically detect

or amplify SEQ ID NO: 1 or SEQ ID NO: 3, or the complement thereof. In yet another aspect, the present invention contemplates such an isolated nucleic acid comprising a nucleotide sequence encoding a fragment of SEQ ID NO: 2 or SEQ ID NO: 4 at least 8 residues in length. The present invention further contemplates a method of hybridizing an oligonucleotide with a nucleic acid of the invention comprising: (a) providing a single-stranded oligonucleotide at least eight nucleotides in length, the oligonucleotide being complementary to a portion of a nucleic acid of the invention; and (b) contacting the oligonucleotide with a sample comprising a nucleic acid of the acid under conditions that permit hybridization of the oligonucleotide with the nucleic acid of the invention.

Isolated nucleic acids which differ from the nucleic acids of the invention due to degeneracy in the genetic code are also within the scope of the invention. For example, a number of amino acids are designated by more than one triplet. Codons that specify the same amino acid, or synonyms (for example, CAU and CAC are synonyms for histidine) may result in "silent" mutations which do not affect the amino acid sequence of the protein. However, it is expected that DNA sequence polymorphisms that do lead to changes in the amino acid sequences of the polypeptides of the invention will exist. One skilled in the art will appreciate that these variations in one or more nucleotides (from less than 1% up to about 3 or 5% or possibly more of the nucleotides) of the nucleic acids encoding a particular protein of the invention may exist among a given species due to natural allelic variation. Any and all such nucleotide variations and resulting amino acid polymorphisms are within the scope of this invention.

Bias in codon choice within genes in a single species appears related to the level of expression of the protein encoded by that gene. Accordingly, the invention encompasses nucleic acid sequences which have been optimized for improved expression in a host cell by altering the frequency of codon usage in the nucleic acid sequence to approach the frequency of preferred codon usage of the host cell. Due to codon degeneracy, it is possible to optimize the nucleotide sequence without affecting the amino acid sequence of an encoded polypeptide. Accordingly, the instant invention relates to any nucleotide sequence that encodes all or a substantial portion of the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4 or other polypeptides of the invention.

The present invention pertains to nucleic acids encoding proteins derived from *E. faecalis* and which have amino acid sequences evolutionarily related to a polypeptide of the invention, wherein "evolutionarily related to", refers to proteins having different amino acid

sequences which have arisen naturally (e.g. by allelic variance or by differential splicing), as well as mutational variants of the proteins of the invention which are derived, for example, by combinatorial mutagenesis.

Fragments of the polynucleotides of the invention encoding a biologically active portion of the subject polypeptides are also within the scope of the invention. As used herein, a fragment of a nucleic acid of the invention encoding an active portion of a polypeptide of the invention refers to a nucleotide sequence having fewer nucleotides than the nucleotide sequence encoding the full length amino acid sequence of a polypeptide of the invention, for example, SEQ ID NO: 2 or SEQ ID NO: 4, and which encodes a polypeptide which retains at least a portion of a biological activity of the full-length protein as defined herein, or alternatively, which is functional as a modulator of the biological activity of the full-length protein. For example, such fragments include a polypeptide containing a domain of the full-length protein from which the polypeptide is derived that mediates the interaction of the protein with another molecule (e.g., polypeptide, DNA, RNA, etc.). In another embodiment, the present invention contemplates an isolated nucleic acid that encodes a polypeptide having a biological activity of a protein having the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4, or alternatively biological activity of histidine tRNA synthetase.

Nucleic acids within the scope of the invention may also contain linker sequences, modified restriction endonuclease sites and other sequences useful for molecular cloning, expression or purification of such recombinant polypeptides.

A nucleic acid encoding a polypeptide of the invention may be obtained from mRNA or genomic DNA from any organism in accordance with protocols described herein, as well as those generally known to those skilled in the art. A cDNA encoding a polypeptide of the invention, for example, may be obtained by isolating total mRNA from an organism, e.g. a bacteria, virus, mammal, etc. Double stranded cDNAs may then be prepared from the total mRNA, and subsequently inserted into a suitable plasmid or bacteriophage vector using any one of a number of known techniques. A gene encoding a polypeptide of the invention may also be cloned using established polymerase chain reaction techniques in accordance with the nucleotide sequence information provided by the invention. In one aspect, the present invention contemplates a method for amplification of a nucleic acid of the invention, or a fragment thereof, comprising: (a) providing a pair of single stranded oligonucleotides, each of which is at least eight nucleotides in length,

complementary to sequences of a nucleic acid of the invention, and wherein the sequences to which the oligonucleotides are complementary are at least ten nucleotides apart; and (b) contacting the oligonucleotides with a sample comprising a nucleic acid comprising the nucleic acid of the invention under conditions which permit amplification of the region located between the pair of oligonucleotides, thereby amplifying the nucleic acid.

Another aspect of the invention relates to the use of nucleic acids of the invention in "antisense therapy". As used herein, antisense therapy refers to administration or *in situ* generation of oligonucleotide probes or their derivatives which specifically hybridize or otherwise bind under cellular conditions with the cellular mRNA and/or genomic DNA encoding one of the polypeptides of the invention so as to inhibit expression of that polypeptide, e.g. by inhibiting transcription and/or translation. The binding may be by conventional base pair complementarity, or, for example, in the case of binding to DNA duplexes, through specific interactions in the major groove of the double helix. In general, antisense therapy refers to the range of techniques generally employed in the art, and includes any therapy which relies on specific binding to oligonucleotide sequences.

An antisense construct of the present invention may be delivered, for example, as an expression plasmid which, when transcribed in the cell, produces RNA which is complementary to at least a unique portion of the mRNA which encodes a polypeptide of the invention. Alternatively, the antisense construct may be an oligonucleotide probe which is generated *ex vivo* and which, when introduced into the cell causes inhibition of expression by hybridizing with the mRNA and/or genomic sequences encoding a polypeptide of the invention. Such oligonucleotide probes may be modified oligonucleotides which are resistant to endogenous nucleases, e.g. exonucleases and/or endonucleases, and are therefore stable *in vivo*. Exemplary nucleic acid molecules for use as antisense oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Patents 5,176,996; 5,264,564; and 5,256,775). Additionally, general approaches to constructing oligomers useful in antisense therapy have been reviewed, for example, by van der Krol et al., (1988) *Biotechniques* 6:958-976; and Stein et al., (1988) *Cancer Res* 48:2659-2668.

In a further aspect, the invention provides double stranded small interfering RNAs (siRNAs), and methods for administering the same. siRNAs decrease or block gene expression. While not wishing to be bound by theory, it is generally thought that siRNAs inhibit gene expression by mediating sequence specific mRNA degradation. RNA

interference (RNAi) is the process of sequence-specific, post-transcriptional gene silencing, particularly in animals and plants, initiated by double-stranded RNA (dsRNA) that is homologous in sequence to the silenced gene (Elbashir et al. Nature 2001; 411(6836): 494-8). Accordingly, it is understood that siRNAs and long dsRNAs having substantial sequence identity to all or a portion of SEQ ID NO: 1 or SEQ ID NO: 3 may be used to inhibit the expression of a nucleic acid of the invention, and particularly when the polynucleotide is expressed in a mammalian or plant cell.

The nucleic acids of the invention may be used as diagnostic reagents to detect the presence or absence of the target DNA or RNA sequences to which they specifically bind, such as for determining the level of expression of a nucleic acid of the invention. In one aspect, the present invention contemplates a method for detecting the presence of a nucleic acid of the invention or a portion thereof in a sample, the method comprising: (a) providing an oligonucleotide at least eight nucleotides in length, the oligonucleotide being complementary to a portion of a nucleic acid of the invention; (b) contacting the oligonucleotide with a sample comprising at least one nucleic acid under conditions that permit hybridization of the oligonucleotide with a nucleic acid comprising a nucleotide sequence complementary thereto; and (c) detecting hybridization of the oligonucleotide to a nucleic acid in the sample, thereby detecting the presence of a nucleic acid of the invention or a portion thereof in the sample. In another aspect, the present invention contemplates a method for detecting the presence of a nucleic acid of the invention or a portion thereof in a sample, the method comprising: (a) providing a pair of single stranded oligonucleotides, each of which is at least eight nucleotides in length, complementary to sequences of a nucleic acid of the invention, and wherein the sequences to which the oligonucleotides are complementary are at least ten nucleotides apart; and (b) contacting the oligonucleotides with a sample comprising at least one nucleic acid under hybridization conditions; (c) amplifying the nucleotide sequence between the two oligonucleotide primers; and (d) detecting the presence of the amplified sequence, thereby detecting the presence of a nucleic acid comprising the nucleic acid of the invention or a portion thereof in the sample.

In another aspect of the invention, the subject nucleic acid is provided in an expression vector comprising a nucleotide sequence encoding a polypeptide of the invention and operably linked to at least one regulatory sequence. It should be understood that the design of the expression vector may depend on such factors as the choice of the host cell to be transformed and/or the type of protein desired to be expressed. The vector's

copy number, the ability to control that copy number and the expression of any other protein encoded by the vector, such as antibiotic markers, should be considered.

The subject nucleic acids may be used to cause expression and over-expression of a polypeptide of the invention in cells propagated in culture, e.g. to produce proteins or polypeptides, including fusion proteins or polypeptides.

This invention pertains to a host cell transfected with a recombinant gene in order to express a polypeptide of the invention. The host cell may be any prokaryotic or eukaryotic cell. For example, a polypeptide of the invention may be expressed in bacterial cells, such as *E. coli*, insect cells (baculovirus), yeast, or mammalian cells. In those instances when the host cell is human, it may or may not be in a live subject. Other suitable host cells are known to those skilled in the art. Additionally, the host cell may be supplemented with tRNA molecules not typically found in the host so as to optimize expression of the polypeptide. Other methods suitable for maximizing expression of the polypeptide will be known to those in the art.

The present invention further pertains to methods of producing the polypeptides of the invention. For example, a host cell transfected with an expression vector encoding a polypeptide of the invention may be cultured under appropriate conditions to allow expression of the polypeptide to occur. The polypeptide may be secreted and isolated from a mixture of cells and medium containing the polypeptide. Alternatively, the polypeptide may be retained cytoplasmically and the cells harvested, lysed and the protein isolated.

A cell culture includes host cells, media and other byproducts. Suitable media for cell culture are well known in the art. The polypeptide may be isolated from cell culture medium, host cells, or both using techniques known in the art for purifying proteins, including ion-exchange chromatography, gel filtration chromatography, ultrafiltration, electrophoresis, and immunoaffinity purification with antibodies specific for particular epitopes of a polypeptide of the invention.

Thus, a nucleotide sequence encoding all or a selected portion of polypeptide of the invention, may be used to produce a recombinant form of the protein via microbial or eukaryotic cellular processes. Ligating the sequence into a polynucleotide construct, such as an expression vector, and transforming or transfecting into hosts, either eukaryotic (yeast, avian, insect or mammalian) or prokaryotic (bacterial cells), are standard procedures. Similar procedures, or modifications thereof, may be employed to prepare recombinant polypeptides of the invention by microbial means or tissue-culture technology.

Expression vehicles for production of a recombinant protein include plasmids and other vectors. For instance, suitable vectors for the expression of a polypeptide of the invention include plasmids of the types: pBR322-derived plasmids, pEMBL-derived plasmids, pEX-derived plasmids, pBTac-derived plasmids and pUC-derived plasmids for expression in prokaryotic cells, such as *E. coli*.

A number of vectors exist for the expression of recombinant proteins in yeast. For instance, YEP24, YIP5, YEP51, YEP52, pYES2, and YRP17 are cloning and expression vehicles useful in the introduction of genetic constructs into *S. cerevisiae* (see, for example, Broach et al., (1983) in *Experimental Manipulation of Gene Expression*, ed. M. Inouye Academic Press, p. 83). These vectors may replicate in *E. coli* due the presence of the pBR322 ori, and in *S. cerevisiae* due to the replication determinant of the yeast 2 micron plasmid. In addition, drug resistance markers such as ampicillin may be used.

In certain embodiments, mammalian expression vectors contain both prokaryotic sequences to facilitate the propagation of the vector in bacteria, and one or more eukaryotic transcription units that are expressed in eukaryotic cells. The pcDNAI/amp, pcDNAI/neo, pRc/CMV, pSV2gpt, pSV2neo, pSV2-dhfr, pTk2, pRSVneo, pMSG, pSVT7, pko-neo and pHyg derived vectors are examples of mammalian expression vectors suitable for transfection of eukaryotic cells. Some of these vectors are modified with sequences from bacterial plasmids, such as pBR322, to facilitate replication and drug resistance selection in both prokaryotic and eukaryotic cells. Alternatively, derivatives of viruses such as the bovine papilloma virus (BPV-1), or Epstein-Barr virus (pHEBo, pREP-derived and p205) can be used for transient expression of proteins in eukaryotic cells. The various methods employed in the preparation of the plasmids and transformation of host organisms are well known in the art. For other suitable expression systems for both prokaryotic and eukaryotic cells, as well as general recombinant procedures, see *Molecular Cloning A Laboratory Manual*, 2nd Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press, 1989) Chapters 16 and 17. In some instances, it may be desirable to express the recombinant protein by the use of a baculovirus expression system. Examples of such baculovirus expression systems include pVL-derived vectors (such as pVL1392, pVL1393 and pVL941), pAcUW-derived vectors (such as pAcUW1), and pBlueBac-derived vectors (such as the ß-gal containing pBlueBac III).

In another variation, protein production may be achieved using *in vitro* translation systems. *In vitro* translation systems are, generally, a translation system which is a cell-free

extract containing at least the minimum elements necessary for translation of an RNA molecule into a protein. An *in vitro* translation system typically comprises at least ribosomes, tRNAs, initiator methionyl-tRNAMet, proteins or complexes involved in translation, e.g., eIF2, eIF3, the cap-binding (CB) complex, comprising the cap-binding protein (CBP) and eukaryotic initiation factor 4F (eIF4F). A variety of *in vitro* translation systems are well known in the art and include commercially available kits. Examples of *in vitro* translation systems include eukaryotic lysates, such as rabbit reticulocyte lysates, rabbit oocyte lysates, human cell lysates, insect cell lysates and wheat germ extracts. Lysates are commercially available from manufacturers such as Promega Corp., Madison, Wis.; Stratagene, La Jolla, Calif.; Amersham, Arlington Heights, Ill.; and GIBCO/BRL, Grand Island, N.Y. *In vitro* translation systems typically comprise macromolecules, such as enzymes, translation, initiation and elongation factors, chemical reagents, and ribosomes. In addition, an *in vitro* transcription system may be used. Such systems typically comprise at least an RNA polymerase holoenzyme, ribonucleotides and any necessary transcription initiation, elongation and termination factors. *In vitro* transcription and translation may be coupled in a one-pot reaction to produce proteins from one or more isolated DNAs.

When expression of a carboxy terminal fragment of a polypeptide is desired, i.e. a truncation mutant, it may be necessary to add a start codon (ATG) to the oligonucleotide fragment containing the desired sequence to be expressed. It is well known in the art that a methionine at the N-terminal position may be enzymatically cleaved by the use of the enzyme methionine aminopeptidase (MAP). MAP has been cloned from *E. coli* (Ben-Bassat et al., (1987) *J. Bacteriol.* 169:751-757) and *Salmonella typhimurium* and its *in vitro* activity has been demonstrated on recombinant proteins (Miller et al., (1987) *PNAS USA* 84:2718-1722). Therefore, removal of an N-terminal methionine, if desired, may be achieved either *in vivo* by expressing such recombinant polypeptides in a host which produces MAP (e.g., *E. coli* or CM89 or *S. cerevisiae*), or *in vitro* by use of purified MAP (e.g., procedure of Miller et al.).

Coding sequences for a polypeptide of interest may be incorporated as a part of a fusion gene including a nucleotide sequence encoding a different polypeptide. The present invention contemplates an isolated nucleic acid comprising a nucleic acid of the invention and at least one heterologous sequence encoding a heterologous peptide linked in frame to the nucleotide sequence of the nucleic acid of the invention so as to encode a fusion protein comprising the heterologous polypeptide. The heterologous polypeptide may be fused to

(a) the C-terminus of the polypeptide encoded by the nucleic acid of the invention, (b) the N-terminus of the polypeptide, or (c) the C-terminus and the N-terminus of the polypeptide. In certain instances, the heterologous sequence encodes a polypeptide permitting the detection, isolation, solubilization and/or stabilization of the polypeptide to which it is fused. In still other embodiments, the heterologous sequence encodes a polypeptide selected from the group consisting of a polyHis tag, myc, HA, GST, protein A, protein G, calmodulin-binding peptide, thioredoxin, maltose-binding protein, poly arginine, poly His-Asp, FLAG, a portion of an immunoglobulin protein, and a transcytosis peptide.

Fusion expression systems can be useful when it is desirable to produce an immunogenic fragment of a polypeptide of the invention. For example, the VP6 capsid protein of rotavirus may be used as an immunologic carrier protein for portions of polypeptide, either in the monomeric form or in the form of a viral particle. The nucleic acid sequences corresponding to the portion of a polypeptide of the invention to which antibodies are to be raised may be incorporated into a fusion gene construct which includes coding sequences for a late vaccinia virus structural protein to produce a set of recombinant viruses expressing fusion proteins comprising a portion of the protein as part of the virion. The Hepatitis B surface antigen may also be utilized in this role as well. Similarly, chimeric constructs coding for fusion proteins containing a portion of a polypeptide of the invention and the poliovirus capsid protein may be created to enhance immunogenicity (see, for example, EP Publication NO: 0259149; and Evans et al., (1989) *Nature* 339:385; Huang et al., (1988) *J. Virol.* 62:3855; and Schlienger et al., (1992) *J. Virol.* 66:2).

Fusion proteins may facilitate the expression and/or purification of proteins. For example, a polypeptide of the invention may be generated as a glutathione-S-transferase (GST) fusion protein. Such GST fusion proteins may be used to simplify purification of a polypeptide of the invention, such as through the use of glutathione-derivatized matrices (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel et al., (N.Y.: John Wiley & Sons, 1991)). In another embodiment, a fusion gene coding for a purification leader sequence, such as a poly-(His)/enterokinase cleavage site sequence at the N-terminus of the desired portion of the recombinant protein, may allow purification of the expressed fusion protein by affinity chromatography using a Ni^{2+} metal resin. The purification leader sequence may then be subsequently removed by treatment with enterokinase to provide the purified protein (e.g., see Hochuli et al., (1987) *J. Chromatography* 411: 177; and Janknecht et al., *PNAS USA* 88:8972).

Techniques for making fusion genes are well known. Essentially, the joining of various DNA fragments coding for different polypeptide sequences is performed in accordance with conventional techniques, employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene may be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments may be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which may subsequently be annealed to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel et al., John Wiley & Sons: 1992).

The present invention further contemplates a transgenic non-human animal having cells which harbor a transgene comprising a nucleic acid of the invention.

In other embodiments, the invention provides for nucleic acids of the invention immobilized onto a solid surface, including, plates, microtiter plates, slides, beads, particles, spheres, films, strands, precipitates, gels, sheets, tubing, containers, capillaries, pads, slices, etc. The nucleic acids of the invention may be immobilized onto a chip as part of an array. The array may comprise one or more polynucleotides of the invention as described herein. In one embodiment, the chip comprises one or more polynucleotides of the invention as part of an array of *E. faecalis* polynucleotide sequences.

In still other embodiments, the invention comprises the sequence of a nucleic acid of the invention in computer readable format. The invention also encompasses a database comprising the sequence of a nucleic acid of the invention.

4. Homology Searching of Nucleotide and Polypeptide Sequences

The nucleotide or amino acid sequences of the invention, including those set forth in the appended Figures, may be used as query sequences against databases such as GenBank, SwissProt, PDB, BLOCKS, and Pima II. These databases contain previously identified and annotated sequences that may be searched for regions of homology (similarity) using BLAST, which stands for Basic Local Alignment Search Tool (Altschul S F (1993) J Mol Evol 36:290-300; Altschul, S F et al (1990) J Mol Biol 215:403-10).

BLAST produces alignments of both nucleotide and amino acid sequences to determine sequence similarity. Because of the local nature of the alignments, BLAST is

especially useful in determining exact matches or in identifying homologs which may be of prokaryotic (bacterial) or eukaryotic (animal, fungal or plant) origin. Other algorithms such as the one described in Smith, R. F. and T. F. Smith (1992; Protein Engineering 5:35-51) may be used when dealing with primary sequence patterns and secondary structure gap penalties. In the usual course using BLAST, sequences have lengths of at least 49 nucleotides and no more than 12% uncalled bases (where N is recorded rather than A, C, G, or T).

The BLAST approach, as detailed in Karlin and Altschul (1993; Proc Nat Acad Sci 90:5873-7) searches matches between a query sequence and a database sequence, to evaluate the statistical significance of any matches found, and to report only those matches which satisfy the user-selected threshold of significance. The threshold is typically set at about 10-25 for nucleotides and about 3-15 for peptides.

5. Analysis of Protein Properties

(a) Analysis of Proteins by Mass Spectrometry

Typically, protein characterization by mass spectroscopy first requires protein isolation followed by either chemical or enzymatic digestion of the protein into smaller peptide fragments, whereupon the peptide fragments may be analyzed by mass spectrometry to obtain a peptide map. Mass spectrometry may also be used to identify post-translational modifications (e.g., phosphorylation, etc.) of a polypeptide.

Various mass spectrometers may be used within the present invention. Representative examples include: triple quadrupole mass spectrometers, magnetic sector instruments (magnetic tandem mass spectrometer, JEOL, Peabody, Mass), ionspray mass spectrometers (Bruins et al., Anal Chem. 59:2642-2647, 1987), electrospray mass spectrometers (including tandem, nano- and nano-electrospray tandem) (Fenn et al., Science 246:64-71, 1989), laser desorption time-of-flight mass spectrometers (Karas and Hillenkamp, Anal. Chem. 60:2299-2301, 1988), and a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (Extrel Corp., Pittsburgh, Mass.).

MALDI ionization is a technique in which samples of interest, in this case peptides and proteins, are co-crystallized with an acidified matrix. The matrix is typically a small molecule that absorbs at a specific wavelength, generally in the ultraviolet (UV) range, and dissipates the absorbed energy thermally. Typically a pulsed laser beam is used to transfer energy rapidly (i.e., a few ns) to the matrix. This transfer of energy causes the matrix to

rapidly dissociate from the MALDI plate surface and results in a plume of matrix and the co-crystallized analytes being transferred into the gas phase. MALDI is considered a "soft-ionization" method that typically results in singly-charged species in the gas phase, most often resulting from a protonation reaction with the matrix. MALDI may be coupled in-line with time of flight (TOF) mass spectrometers. TOF detectors are based on the principle that an analyte moves with a velocity proportional to its mass. Analytes of higher mass move slower than analytes of lower mass and thus reach the detector later than lighter analytes. The present invention contemplates a composition comprising a polypeptide of the invention and a matrix suitable for mass spectrometry. In certain instances, the matrix is a nicotinic acid derivative or a cinnamic acid derivative.

MALDI-TOF MS is easily performed with modern mass spectrometers. Typically the samples of interest, in this case peptides or proteins, are mixed with a matrix and spotted onto a polished stainless steel plate (MALDI plate). Commercially available MALDI plates can presently hold up to 1536 samples per plate. Once spotted with sample, the MALDI sample plate is then introduced into the vacuum chamber of a MALDI mass spectrometer. The pulsed laser is then activated and the mass to charge ratios of the analytes are measured utilizing a time of flight detector. A mass spectrum representing the mass to charge ratios of the peptides/proteins is generated.

As mentioned above, MALDI can be utilized to measure the mass to charge ratios of both proteins and peptides. In the case of proteins, a mixture of intact protein and matrix are co-crystallized on a MALDI target (Karas, M. and Hillenkamp, F. Anal. Chem. 1988, 60 (20) 2299-2301). The spectrum resulting from this analysis is employed to determine the molecular weight of a whole protein. This molecular weight can then be compared to the theoretical weight of the protein and utilized in characterizing the analyte of interest, such as whether or not the protein has undergone post-translational modifications (e.g., example phosphorylation).

In certain embodiments, MALDI mass spectrometry is used for determination of peptide maps of digested proteins. The peptide masses are measured accurately using a MALDI-TOF or a MALDI-Q-Star mass spectrometer, with detection precision down to the low ppm (parts per million) level. The ensemble of the peptide masses observed in a protein digest, such as a tryptic digest, may be used to search protein/DNA databases in a method called peptide mass fingerprinting. In this approach, protein entries in a database are ranked according to the number of experimental peptide masses that match the

predicted trypsin digestion pattern. Commercially available software utilizes a search algorithm that provides a scoring scheme based on the size of the databases, the number of matching peptides, and the different peptides. Depending on the number of peptides observed, the accuracy of the measurement, and the size of the genome of the particular species, unambiguous protein identification may be obtained.

Statistical analysis may be performed upon each protein match to determine the validity of the match. Typical constraints include error tolerances within 0.1 Da for monoisotopic peptide masses, cysteines may be alkylated and searched as carboxyamidomethyl modifications, 0 or 1 missed enzyme cleavages, and no methionine oxidations allowed. Identified proteins may be stored automatically in a relational database with software links to SDS-PAGE images and ligand sequences. Often even a partial peptide map is specific enough for identification of the protein. If no protein match is found, a more error-tolerant search can be used, for example using fewer peptides or allowing a larger margin error with respect to mass accuracy.

Other mass spectroscopy methods such as tandem mass spectrometry or post source decay may be used to obtain sequence information about proteins that cannot be identified by peptide mass mapping, or to confirm the identity of proteins that are tentatively identified by an error-tolerant peptide mass search described above. (Griffin et al, Rapid Commun. Mass. Spectrom. 1995, 9, 1546-51).

(b) Analysis of Proteins by Nuclear Magnetic Resonance (NMR)

NMR may be used to characterize the structure of a polypeptide in accordance with the methods of the invention. In particular, NMR can be used, for example, to determine the three dimensional structure, the conformational state, the aggregation level, the state of protein folding/unfolding or the dynamic properties of a polypeptide. For example, the present invention contemplates a method for determining three dimensional structure information of a polypeptide of the invention, the method comprising: (a) generating a purified isotopically labeled polypeptide of the invention; and (b) subjecting the polypeptide to NMR spectroscopic analysis, thereby determining information about its three dimensional structure.

Interaction between a polypeptide and another molecule can also be monitored using NMR. Thus, the invention encompasses methods for detecting, designing and characterizing interactions between a polypeptide and another molecule, including polypeptides, nucleic acids and small molecules, utilizing NMR techniques. For example,

the present invention contemplates a method for determining three dimensional structure information of a polypeptide of the invention, or a fragment thereof, while the polypeptide is complexed with another molecule, the method comprising: (a) generating a purified isotopically labeled polypeptide of the invention, or a fragment thereof; (b) forming a complex between the polypeptide and the other molecule; and (c) subjecting the complex to NMR spectroscopic analysis, thereby determining information about the three dimensional structure of the polypeptide. In another aspect, the present invention contemplates a method for identifying compounds that bind to a polypeptide of the invention, or a fragment thereof, the method comprising: (a) generating a first NMR spectrum of an isotopically labeled polypeptide of the invention, or a fragment thereof; (b) exposing the polypeptide to one or more chemical compounds; (c) generating a second NMR spectrum of the polypeptide which has been exposed to one or more chemical compounds; and (d) comparing the first and second spectra to determine differences between the first and the second spectra, wherein the differences are indicative of one or more compounds that have bound to the polypeptide.

Briefly, the NMR technique involves placing the material to be examined (usually in a suitable solvent) in a powerful magnetic field and irradiating it with radio frequency (rf) electromagnetic radiation. The nuclei of the various atoms will align themselves with the magnetic field until energized by the rf radiation. They then absorb this resonant energy and re-radiate it at a frequency dependent on i) the type of nucleus and ii) its atomic environment. Moreover, resonant energy may be passed from one nucleus to another, either through bonds or through three-dimensional space, thus giving information about the environment of a particular nucleus and nuclei in its vicinity.

However, it is important to recognize that not all nuclei are NMR active. Indeed, not all isotopes of the same element are active. For example, whereas "ordinary" hydrogen, ^{1}H, is NMR active, heavy hydrogen (deuterium), ^{2}H, is not active in the same way. Thus, any material that normally contains ^{1}H hydrogen may be rendered "invisible" in the hydrogen NMR spectrum by replacing all or almost all the ^{1}H hydrogens with ^{2}H. It is for this reason that NMR spectroscopic analyses of water-soluble materials frequently are performed in $^{2}H_2O$ (or deuterium) to eliminate the water signal.

Conversely, "ordinary" carbon, ^{12}C, is NMR inactive whereas the stable isotope, ^{13}C, present to about 1% of total carbon in nature, is active. Similarly, while "ordinary" nitrogen, ^{14}N, is NMR active, it has undesirable properties for NMR and resonates at a

different frequency from the stable isotope ^{15}N, present to about 0.4% of total nitrogen in nature.

By labeling proteins with ^{15}N and $^{15}N/^{13}C$, it is possible to conduct analytical NMR of macromolecules with weights of 15 kD and 40 kD, respectively. More recently, partial deuteration of the protein in addition to ^{13}C- and ^{15}N-labeling has increased the possible weight of proteins and protein complexes for NMR analysis still further, to approximately 60-70 kD. See Shan et al., J. Am. Chem.Soc., 118:6570-6579 (1996); L.E. Kay, Methods Enzymol., 339:174-203 (2001); and K.H. Gardner & L.E. Kay, Annu Rev Biophys Biomol Struct., 27:357-406 (1998); and references cited therein.

Isotopic substitution may be accomplished by growing a bacterium or yeast or other type of cultured cells, transformed by genetic engineering to produce the protein of choice, in a growth medium containing ^{13}C-, ^{15}N- and/or ^{2}H-labeled substrates. In certain instances, bacterial growth media consists of ^{13}C-labeled glucose and/or ^{15}N-labeled ammonium salts dissolved in D_2O where necessary. Kay, L. et al., Science, 249:411 (1990) and references therein and Bax, A., J. Am. Chem. Soc., 115, 4369 (1993). More recently, isotopically labeled media especially adapted for the labeling of bacterially produced macromolecules have been described. See U.S. Pat. No. 5,324,658.

The goal of these methods has been to achieve universal and/or random isotopic enrichment of all of the amino acids of the protein. By contrast, other methods allow only certain residues to be relatively enriched in ^{1}H, ^{2}H, ^{13}C and ^{15}N. For example, Kay et al., J. Mol. Biol., 263, 627-636 (1996) and Kay et al., J. Am. Chem. Soc., 119, 7599-7600 (1997) have described methods whereby isoleucine, alanine, valine and leucine residues in a protein may be labeled with ^{2}H, ^{13}C and ^{15}N, and may be specifically labeled with ^{1}H at the terminal methyl position. In this way, study of the proton-proton interactions between some amino acids may be facilitated. Similarly, a cell-free system has been described by Yokoyama et al., J. Biomol. NMR, 6(2), 129-134 (1995), wherein a transcription-translation system derived from *E. coli* was used to express human Ha-Ras protein incorporating ^{15}N into serine and/or aspartic acid.

Techniques for producing isotopically labeled proteins and macromolecules, such as glycoproteins, in mammalian or insect cells have been described. See U.S. Pat. Nos. 5,393,669 and 5,627,044; Weller, C. T., Biochem., 35, 8815-23 (1996) and Lustbader, J. W., J.Biomol. NMR, 7, 295-304 (1996). Other methods for producing polypeptides and other molecules with labels appropriate for NMR are known in the art.

The present invention contemplates using a variety of solvents which are appropriate for NMR. For ^1H NMR, a deuterium lock solvent may be used. Exemplary deuterium lock solvents include acetone (CD_3COCD_3), chloroform ($CDCl_3$), dichloro methane (CD_2Cl_2), methylnitrile (CD_3CN), benzene (C_6D_6), water (D_2O), diethylether (($CD_3CD_2)_2O$), dimethylether (($CD_3)_2O$), N,N-dimethylformamide (($CD_3)_2NCDO$), dimethyl sulfoxide (CD_3SOCD_3), ethanol (CD_3CD_2OD), methanol (CD_3OD), tetrahydrofuran (C_4D_8O), toluene ($C_6D_5CD_3$), pyridine (C_5D_5N) and cyclohexane (C_6H_{12}). For example, the present invention contemplates a composition comprising a polypeptide of the invention and a deuterium lock solvent.

The 2-dimensional ^1H-^{15}N HSQC (Heteronuclear Single Quantum Correlation) spectrum provides a diagnostic fingerprint of conformational state, aggregation level, state of protein folding, and dynamic properties of a polypeptide (Yee et al, PNAS 99, 1825-30 (2002)). Polypeptides in aqueous solution usually populate an ensemble of 3-dimensional structures which can be determined by NMR. When the polypeptide is a stable globular protein or domain of a protein, then the ensemble of solution structures is one of very closely related conformations. In this case, one peak is expected for each non-proline residue with a dispersion of resonance frequencies with roughly equal intensity. Additional pairs of peaks from side-chain NH_2 groups are also often observed, and correspond to the approximate number of Gln and Asn residues in the protein. This type of HSQC spectra usually indicates that the protein is amenable to structure determination by NMR methods.

If the HSQC spectrum shows well-dispersed peaks but there are either too few or too many in number, and/or the peak intensities differ throughout the spectrum, then the protein likely does not exist in a single globular conformation. Such spectral features are indicative of conformational heterogeneity with slow or nonexistent inter-conversion between states (too many peaks) or the presence of dynamic processes on an intermediate timescale that can broaden and obscure the NMR signals. Proteins with this type of spectrum can sometimes be stabilized into a single conformation by changing either the protein construct, the solution conditions, temperature or by binding of another molecule.

The ^1H-^{15}N HSQC can also indicate whether a protein has formed large nonspecific aggregates or has dynamic properties. Alternatively, proteins that are largely unfolded, e.g., having very little regular secondary structure, result in ^1H-^{15}N HSQC spectra in which the peaks are all very narrow and intense, but have very little spectral dispersion in the ^{15}N-dimension. This reflects the fact that many or most of the amide groups of amino acids in

unfolded polypeptides are solvent exposed and experience similar chemical environments resulting in similar ^{1}H chemical shifts.

The use of the ^{1}H-^{15}N HSQC, can thus allow the rapid characterization of the conformational state, aggregation level, state of protein folding, and dynamic properties of a polypeptide. Additionally, other 2D spectra such as ^{1}H-^{13}C HSQC, or HNCO spectra can also be used in a similar manner. Further use of the ^{1}H-^{15}N HSQC combined with relaxation measurements can reveal the molecular rotational correlation time and dynamic properties of polypeptides. The rotational correlation time is proportional to size of the protein and therefore can reveal if it forms specific homo-oligomers such as homodimers, homotetramers, etc.

The structure of stable globular proteins can be determined through a series of well-described procedures. For a general review of structure determination of globular proteins in solution by NMR spectroscopy, see Wüthrich, Science 243: 45-50 (1989). See also, Billeter et al., J. Mol. Biol. 155: 321-346 (1982). Current methods for structure determination usually require the complete or nearly complete sequence-specific assignment of ^{1}H-resonance frequencies of the protein and subsequent identification of approximate inter-hydrogen distances (from nuclear Overhauser effect (NOE) spectra) for use in restrained molecular dynamics calculations of the protein conformation. One approach for the analysis of NMR resonance assignments was first outlined by Wüthrich, Wagner and co-workers (Wüthrich, "NMR or proteins and nucleic acids" Wiley, New York, New York (1986); Wüthrich, Science 243: 45-50 (1989); Billeter et al., J. Mol. Biol. 155: 321-346 (1982)). Newer methods for determining the structures of globular proteins include the use of residual dipolar coupling restraints (Tian et al., J Am Chem Soc. 2001 Nov 28;123(47):11791-6; Bax et al, Methods Enzymol. 2001;339:127-74) and empirically derived conformational restraints (Zweckstetter & Bax, J Am Chem Soc. 2001 Sep 26;123(38):9490-1). It has also been shown that it may be possible to determine structures of globular proteins using only un-assigned NOE measurements. NMR may also be used to determine ensembles of many inter-converting, unfolded conformations (Choy and Forman-Kay, J Mol Biol. 2001 May 18;308(5):1011-32).

NMR analysis of a polypeptide in the presence and absence of a test compound (e.g., a polypeptide, nucleic acid or small molecule) may be used to characterize interactions between a polypeptide and another molecule. Because the ^{1}H-^{15}N HSQC spectrum and other simple 2D NMR experiments can be obtained very quickly (on the

order of minutes depending on protein concentration and NMR instrumentation), they are very useful for rapidly testing whether a polypeptide is able to bind to another molecule. Changes in the resonance frequency (in one or both dimensions) of one or more peaks in the HSQC spectrum indicate an interaction with another molecule. Often only a subset of the peaks will have changes in resonance frequency upon binding to anther molecule, allowing one to map onto the structure those residues directly involved in the interaction or involved in conformational changes as a result of the interaction. If the interacting molecule is relatively large (protein or nucleic acid) the peak widths will also broaden due to the increased rotational correlation time of the complex. In some cases the peaks involved in the interaction may actually disappear from the NMR spectrum if the interacting molecule is in intermediate exchange on the NMR timescale (i.e., exchanging on and off the polypeptide at a frequency that is similar to the resonance frequency of the monitored nuclei).

To facilitate the acquisition of NMR data on a large number of compounds (e.g., a library of synthetic or naturally-occurring small organic compounds), a sample changer may be employed. Using the sample changer, a larger number of samples, numbering 60 or more, may be run unattended. To facilitate processing of the NMR data, computer programs are used to transfer and automatically process the multiple one-dimensional NMR data.

In one embodiment, the invention provides a screening method for identifying small molecules capable of interacting with a polypeptide of the invention. In one example, the screening process begins with the generation or acquisition of either a T_2-filtered or a diffusion-filtered one-dimensional proton spectrum of the compound or mixture of compounds. Means for generating T_2-filtered or diffusion-filtered one-dimensional proton spectra are well known in the art (see, e.g., S. Meiboom and D. Gill, Rev. Sci. Instrum. 29:688(1958), S. J. Gibbs and C. S. Johnson, Jr. J. Main. Reson. 93:395-402 (1991) and A. S. Altieri, et al. J. Am. Chem. Soc. 117: 7566-7567 (1995)).

Following acquisition of the first spectrum for the molecules, the ^{15}N- or ^{13}C-labeled polypeptide is exposed to one or more molecules. Where more than one test compound is to be tested simultaneously, it is preferred to use a library of compounds such as a plurality of small molecules. Such molecules are typically dissolved in perdeuterated dimethylsulfoxide. The compounds in the library may be purchased from vendors or created according to desired needs.

Individual compounds may be selected inter alia on the basis of size and molecular diversity for maximizing the possibility of discovering compounds that interact with widely diverse binding sites of a polypeptide of the invention.

The NMR screening process of the present invention utilizes a range of test compound concentrations, e.g., from about 0.05 to about 1.0 mM. At those exemplary concentrations, compounds which are acidic or basic may significantly change the pH of buffered protein solutions. Chemical shifts are sensitive to pH changes as well as direct binding interactions, and false-positive chemical shift changes, which are not the result of test compound binding but of changes in pH, may therefore be observed. It may therefore be necessary to ensure that the pH of the buffered solution does not change upon addition of the test compound.

Following exposure of the test compounds to a polypeptide (e.g., the target molecule for the experiment) a second one-dimensional T_2- or diffusion-filtered spectrum is generated. For the T_2-filtered approach, that second spectrum is generated in the same manner as set forth above. The first and second spectra are then compared to determine whether there are any differences between the two spectra. Differences in the one-dimensional T_2-filtered spectra indicate that the compound is binding to, or otherwise interacting with, the target molecule. Those differences are determined using standard procedures well known in the art. For the diffusion-filtered method, the second spectrum is generated by looking at the spectral differences between low and high gradient strengths--thus selecting for those compounds whose diffusion rates are comparable to that observed in the absence of target molecule.

To discover additional molecules that bind to the protein, molecules are selected for testing based on the structure/activity relationships from the initial screen and/or structural information on the initial leads when bound to the protein. By way of example, the initial screening may result in the identification of compounds, all of which contain an aromatic ring. The second round of screening would then use other aromatic molecules as the test compounds.

In another embodiment, the methods of the invention utilize a process for detecting the binding of one ligand to a polypeptide in the presence of a second ligand. In accordance with this embodiment, a polypeptide is bound to the second ligand before exposing the polypeptide to the test compounds.

For more information on NMR methods encompassed by the present invention, see also: U.S. Patent Nos. 5,668,734; 6,194,179; 6,162,627; 6,043,024; 5,817,474; 5,891,642; 5,989,827; 5,891,643; 6,077,682; WO 00/05414; WO 99/22019; Cavanagh, et al., Protein NMR Spectroscopy, Principles and Practice, 1996, Academic Press; Clore, et al., NMR of Proteins. In Topics in Molecular and Structural Biology, 1993, S. Neidle, Fuller, W., and Cohen, J.S., eds., Macmillan Press, Ltd., London; and Christendat et al., Nature Structural Biology 7: 903-909 (2000).

(c) Analysis of Proteins by X-ray Crystallography

(i) X-ray Structure Determination

Exemplary methods for obtaining the three dimensional structure of the crystalline form of a molecule or complex are described herein and, in view of this specification, variations on these methods will be apparent to those skilled in the art (see Ducruix and Geige 1992, IRL Press, Oxford, England).

A variety of methods involving x-ray crystallography are contemplated by the present invention. For example, the present invention contemplates producing a crystallized polypeptide of the invention, or a fragment thereof, by: (a) introducing into a host cell an expression vector comprising a nucleic acid encoding for a polypeptide of the invention, or a fragment thereof; (b) culturing the host cell in a cell culture medium to express the polypeptide or fragment; (c) isolating the polypeptide or fragment from the cell culture; and (d) crystallizing the polypeptide or fragment thereof. Alternatively, the present invention contemplates determining the three dimensional structure of a crystallized polypeptide of the invention, or a fragment thereof, by: (a) crystallizing a polypeptide of the invention, or a fragment thereof, such that the crystals will diffract x-rays to a resolution of 3.5 Å or better; and (b) analyzing the polypeptide or fragment by x-ray diffraction to determine the three-dimensional structure of the crystallized polypeptide.

X-ray crystallography techniques generally require that the protein molecules be available in the form of a crystal. Crystals may be grown from a solution containing a purified polypeptide of the invention, or a fragment thereof (e.g., a stable domain), by a variety of conventional processes. These processes include, for example, batch, liquid, bridge, dialysis, vapour diffusion (e.g., hanging drop or sitting drop methods). (See for example, McPherson, 1982 John Wiley, New York; McPherson, 1990, Eur. J. Biochem. 189: 1-23; Webber. 1991, Adv. Protein Chem. 41:1-36).

In certain embodiments, native crystals of the invention may be grown by adding precipitants to the concentrated solution of the polypeptide. The precipitants are added at a concentration just below that necessary to precipitate the protein. Water may be removed by controlled evaporation to produce precipitating conditions, which are maintained until crystal growth ceases.

The formation of crystals is dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions or ligands to the protein. In addition, the sequence of the polypeptide being crystallized will have a significant affect on the success of obtaining crystals. Many routine crystallization experiments may be needed to screen all these parameters for the few combinations that might give crystal suitable for x-ray diffraction analysis (See, for example, Jancarik, J & Kim, S.H., J. Appl. Cryst. 1991 24: 409-411).

Crystallization robots may automate and speed up the work of reproducibly setting up large number of crystallization experiments. Once some suitable set of conditions for growing the crystal are found, variations of the condition may be systematically screened in order to find the set of conditions which allows the growth of sufficiently large, single, well ordered crystals. In certain instances, a polypeptide of the invention is co-crystallized with a compound that stabilizes the polypeptide.

A number of methods are available to produce suitable radiation for x-ray diffraction. For example, x-ray beams may be produced by synchrotron rings where electrons (or positrons) are accelerated through an electromagnetic field while traveling at close to the speed of light. Because the admitted wavelength may also be controlled, synchrotrons may be used as a tunable x-ray source (Hendrickson WA., Trends Biochem Sci 2000 Dec; 25(12):637-43). For less conventional Laue diffraction studies, polychromatic x-rays covering a broad wavelength window are used to observe many diffraction intensities simultaneously (Stoddard, B. L., Curr. Opin. Struct Biol 1998 Oct; 8(5):612-8). Neutrons may also be used for solving protein crystal structures (Gutberlet T, Heinemann U & Steiner M., Acta Crystallogr D 2001;57: 349-54).

Before data collection commences, a protein crystal may be frozen to protect it from radiation damage. A number of different cryo-protectants may be used to assist in freezing the crystal, such as methyl pentanediol (MPD), isopropanol, ethylene glycol, glycerol, formate, citrate, mineral oil, or a low-molecular-weight polyethylene glycol (PEG). The present invention contemplates a composition comprising a polypeptide of the invention

and a cryo-protectant. As an alternative to freezing the crystal, the crystal may also be used for diffraction experiments performed at temperatures above the freezing point of the solution. In these instances, the crystal may be protected from drying out by placing it in a narrow capillary of a suitable material (generally glass or quartz) with some of the crystal growth solution included in order to maintain vapour pressure.

X-ray diffraction results may be recorded by a number of ways know to one of skill in the art. Examples of area electronic detectors include charge coupled device detectors, multi-wire area detectors and phosphoimager detectors (Amemiya, Y, 1997. Methods in Enzymology, Vol. 276. Academic Press, San Diego, pp. 233-243; Westbrook, E. M., Naday, I. 1997. Methods in Enzymology, Vol. 276. Academic Press, San Diego, pp. 244-268; 1997. Kahn, R. & Fourme, R. Methods in Enzymology, Vol. 276. Academic Press, San Diego, pp. 268-286).

A suitable system for laboratory data collection might include a Bruker AXS Proteum R system, equipped with a copper rotating anode source, Confocal Max-Flux™ optics and a SMART 6000 charge coupled device detector. Collection of x-ray diffraction patterns are well documented by those skilled in the art (See, for example, Ducruix and Geige, 1992, IRL Press, Oxford, England).

The theory behind diffraction by a crystal upon exposure to x-rays is well known. Because phase information is not directly measured in the diffraction experiment, and is needed to reconstruct the electron density map, methods that can recover this missing information are required. One method of solving structures *ab initio* are the real / reciprocal space cycling techniques. Suitable real / reciprocal space cycling search programs include shake-and-bake (Weeks CM, DeTitta GT, Hauptman HA, Thuman P, Miller R Acta Crystallogr A 1994; V50: 210-20).

Other methods for deriving phases may also be needed. These techniques generally rely on the idea that if two or more measurements of the same reflection are made where strong, measurable, differences are attributable to the characteristics of a small subset of the atoms alone, then the contributions of other atoms can be, to a first approximation, ignored, and positions of these atoms may be determined from the difference in scattering by one of the above techniques. Knowing the position and scattering characteristics of those atoms, one may calculate what phase the overall scattering must have had to produce the observed differences.

One version of this technique is isomorphous replacement technique, which requires the introduction of new, well ordered, x-ray scatterers into the crystal. These additions are usually heavy metal atoms, (so that they make a significant difference in the diffraction pattern); and if the additions do not change the structure of the molecule or of the crystal cell, the resulting crystals should be isomorphous. Isomorphous replacement experiments are usually performed by diffusing different heavy-metal metals into the channels of a pre-existing protein crystal. Growing the crystal from protein that has been soaked in the heavy atom is also possible (Petsko, G.A., 1985. Methods in Enzymology, Vol. 114. Academic Press, Orlando, pp. 147-156). Alternatively, the heavy atom may also be reactive and attached covalently to exposed amino acid side chains (such as the sulfur atom of cysteine) or it may be associated through non-covalent interactions. It is sometimes possible to replace endogenous light metals in metallo-proteins with heavier ones, e.g., zinc by mercury, or calcium by samarium (Petsko, G.A., 1985. Methods in Enzymology, Vol. 114. Academic Press, Orlando, pp. 147-156). Exemplary sources for such heavy compounds include, without limitation, sodium bromide, sodium selenate, trimethyl lead acetate, mercuric chloride, methyl mercury acetate, platinum tetracyanide, platinum tetrachloride, nickel chloride, and europium chloride.

A second technique for generating differences in scattering involves the phenomenon of anomalous scattering. X-rays that cause the displacement of an electron in an inner shell to a higher shell are subsequently rescattered, but there is a time lag that shows up as a phase delay. This phase delay is observed as a (generally quite small) difference in intensity between reflections known as Friedel mates that would be identical if no anomalous scattering were present. A second effect related to this phenomenon is that differences in the intensity of scattering of a given atom will vary in a wavelength dependent manner, given rise to what are known as dispersive differences. In principle anomalous scattering occurs with all atoms, but the effect is strongest in heavy atoms, and may be maximized by using x-rays at a wavelength where the energy is equal to the difference in energy between shells. The technique therefore requires the incorporation of some heavy atom much as is needed for isomorphous replacement, although for anomalous scattering a wider variety of atoms are suitable, including lighter metal atoms (copper, zinc, iron) in metallo-proteins. One method for preparing a protein for anomalous scattering involves replacing the methionine residues in whole or in part with selenium containing seleno-methionine. Soaks with halide salts such as bromides and other non-reactive ions

may also be effective (Dauter Z, Li M, Wlodawer A., Acta Crystallogr D 2001; 57: 239-49).

In another process, known as multiple anomalous scattering or MAD, two to four suitable wavelengths of data are collected. (Hendrickson, W.A. and Ogata, C.M. 1997 Methods in Enzymology 276, 494 – 523). Phasing by various combinations of single and multiple isomorphous and anomalous scattering are possible too. For example, SIRAS (single isomorphous replacement with anomalous scattering) utilizes both the isomorphous and anomalous differences for one derivative to derive phases. More traditionally, several different heavy atoms are soaked into different crystals to get sufficient phase information from isomorphous differences while ignoring anomalous scattering, in the technique known as multiple isomorphous replacement (MIR) (Petsko, G.A., 1985. Methods in Enzymology, Vol. 114. Academic Press, Orlando, pp. 147-156).

Additional restraints on the phases may be derived from density modification techniques. These techniques use either generally known features of electron density distribution or known facts about that particular crystal to improve the phases. For example, because protein regions of the crystal scatter more strongly than solvent regions, solvent flattening/flipping may be used to adjust phases to make solvent density a uniform flat value (Zhang, K. Y. J., Cowtan, K. and Main, P. Methods in Enzymology 277, 1997 Academic Press, Orlando pp 53-64). If more than one molecule of the protein is present in the asymmetric unit, the fact that the different molecules should be virtually identical may be exploited to further reduce phase error using non-crystallographic symmetry averaging (Villieux, F. M. D. and Read, R. J. Methods in Enzymology 277, 1997 Academic Press, Orlando pp18-52). Suitable programs for performing these processes include DM and other programs of the CCP4 suite (Collaborative Computational Project, Number 4. 1994. Acta Cryst. D50, 760-763) and CNX.

The unit cell dimensions, symmetry, vector amplitude and derived phase information can be used in a Fourier transform function to calculate the electron density in the unit cell, i.e., to generate an experimental electron density map. This may be accomplished using programs of the CNX or CCP4 packages. The resolution is measured in Ångstrom (Å) units, and is closely related to how far apart two objects need to be before they can be reliably distinguished. The smaller this number is, the higher the resolution and therefore the greater the amount of detail that can be seen. Preferably, crystals of the

invention diffract x-rays to a resolution of better than about 4.0, 3.5, 3.0, 2.5, 2.0, 1.5, 1.0, 0.5 Å or better.

As used herein, the term "modeling" includes the quantitative and qualitative analysis of molecular structure and/or function based on atomic structural information and interaction models. The term "modeling" includes conventional numeric-based molecular dynamic and energy minimization models, interactive computer graphic models, modified molecular mechanics models, distance geometry and other structure-based constraint models.

Model building may be accomplished by either the crystallographer using a computer graphics program such as TURBO or O (Jones, TA. et al., Acta Crystallogr. A47, 100-119, 1991) or, under suitable circumstances, by using a fully automated model building program, such as wARP (Anastassis Perrakis, Richard Morris & Victor S. Lamzin; Nature Structural Biology, May 1999 Volume 6 Number 5 pp 458 – 463) or MAID (Levitt, D. G., Acta Crystallogr. D 2001 V57: 1013-9). This structure may be used to calculate model-derived diffraction amplitudes and phases. The model-derived and experimental diffraction amplitudes may be compared and the agreement between them can be described by a parameter referred to as R-factor. A high degree of correlation in the amplitudes corresponds to a low R-factor value, with 0.0 representing exact agreement and 0.59 representing a completely random structure. Because the R-factor may be lowered by introducing more free parameters into the model, an unbiased, cross-correlated version of the R-factor known as the R-free gives a more objective measure of model quality. For the calculation of this parameter a subset of reflections (generally around 10%) are set aside at the beginning of the refinement and not used as part of the refinement target. These reflections are then compared to those predicted by the model (Kleywegt GJ, Brunger AT, Structure 1996 Aug 15;4(8):897-904).

The model may be improved using computer programs that maximize the probability that the observed data was produced from the predicted model, while simultaneously optimizing the model geometry. For example, the CNX program may be used for model refinement, as can the XPLOR program (1992, Nature 355:472-475, G.N. Murshudov, A.A.Vagin and E.J.Dodson, (1997) Acta Cryst. D 53, 240-255). In order to maximize the convergence radius of refinement, simulated annealing refinement using torsion angle dynamics may be employed in order to reduce the degrees of freedom of motion of the model (Adams PD, Pannu NS, Read RJ, Brunger AT., Proc Natl Acad Sci U

S A 1997 May 13;94(10):5018-23). Where experimental phase information is available (e.g. where MAD data was collected) Hendrickson-Lattman phase probability targets may be employed. Isotropic or anisotropic domain, group or individual temperature factor refinement, may be used to model variance of the atomic position from its mean. Well defined peaks of electron density not attributable to protein atoms are generally modeled as water molecules. Water molecules may be found by manual inspection of electron density maps, or with automatic water picking routines. Additional small molecules, including ions, cofactors, buffer molecules or substrates may be included in the model if sufficiently unambiguous electron density is observed in a map.

In general, the R-free is rarely as low as 0.15 and may be as high as 0.35 or greater for a reasonably well-determined protein structure. The residual difference is a consequence of approximations in the model (inadequate modeling of residual structure in the solvent, modeling atoms as isotropic Gaussian spheres, assuming all molecules are identical rather than having a set of discrete conformers, etc.) and errors in the data (Lattman EE., Proteins 1996; 25: i-ii). In refined structures at high resolution, there are usually no major errors in the orientation of individual residues, and the estimated errors in atomic positions are usually around 0.1 - 0.2 up to 0.3 Å.

The three dimensional structure of a new crystal may be modeled using molecular replacement. The term "molecular replacement" refers to a method that involves generating a preliminary model of a molecule or complex whose structure coordinates are unknown, by orienting and positioning a molecule whose structure coordinates are known within the unit cell of the unknown crystal, so as best to account for the observed diffraction pattern of the unknown crystal. Phases may then be calculated from this model and combined with the observed amplitudes to give an approximate Fourier synthesis of the structure whose coordinates are unknown. This, in turn, can be subject to any of the several forms of refinement to provide a final, accurate structure of the unknown crystal. Lattman, E., "Use of the Rotation and Translation Functions", in Methods in Enzymology, 115, pp. 55-77 (1985); M. G. Rossmann, ed., "The Molecular Replacement Method", Int. Sci. Rev. Ser., No. 13, Gordon & Breach, New York, (1972).

Commonly used computer software packages for molecular replacement are CNX, X-PLOR (Brunger 1992, Nature 355: 472-475), AMoRE (Navaza, 1994, Acta Crystallogr. A50:157-163), the CCP4 package, the MERLOT package (P.M.D. Fitzgerald, J. Appl. Cryst., Vol. 21, pp. 273-278, 1988) and XTALVIEW (McCree et al (1992) J. Mol. Graphics

10: 44-46). The quality of the model may be analyzed using a program such as PROCHECK or 3D-Profiler (Laskowski et al 1993 J. Appl. Cryst. 26:283-291; Luthy R. et al, Nature 356: 83-85, 1992; and Bowie, J.U. et al, Science 253: 164-170, 1991).

Homology modeling (also known as comparative modeling or knowledge-based modeling) methods may also be used to develop a three dimensional model from a polypeptide sequence based on the structures of known proteins. The method utilizes a computer model of a known protein, a computer representation of the amino acid sequence of the polypeptide with an unknown structure, and standard computer representations of the structures of amino acids. This method is well known to those skilled in the art (Greer, 1985, Science 228, 1055; Bundell et al 1988, Eur. J. Biochem. 172, 513; Knighton et al., 1992, Science 258:130-135, http://biochem.vt.edu/courses/-modeling/homology.htm). Computer programs that can be used in homology modeling are QUANTA and the Homology module in the Insight II modeling package distributed by Molecular Simulations Inc, or MODELLER (Rockefeller University, www.iucr.ac.uk/sinris-top/logical/prg-modeller.html).

Once a homology model has been generated it is analyzed to determine its correctness. A computer program available to assist in this analysis is the Protein Health module in QUANTA which provides a variety of tests. Other programs that provide structure analysis along with output include PROCHECK and 3D-Profiler (Luthy R. et al, Nature 356: 83-85, 1992; and Bowie, J.U. et al, Science 253: 164-170, 1991). Once any irregularities have been resolved, the entire structure may be further refined.

Other molecular modeling techniques may also be employed in accordance with this invention. See, e.g., Cohen, N. C. *et al*, J. Med. Chem., 33, pp. 883-894 (1990). See also, Navix, M. A. and M. A. Marko, Current Opinions in Structural Biology, 2, pp. 202-210 (1992).

Under suitable circumstances, the entire process of solving a crystal structure may be accomplished in an automated fashion by a system such as ELVES (http://ucxray.berkeley.edu/~jamesh/elves/index.html) with little or no user intervention.

(ii) X-ray Structure

The present invention provides methods for determining some or all of the structural coordinates for amino acids of a polypeptide of the invention, or a complex thereof.

In another aspect, the present invention provides methods for identifying a druggable region of a polypeptide of the invention. For example, one such method

includes: (a) obtaining crystals of a polypeptide of the invention or a fragment thereof such that the three dimensional structure of the crystallized protein can be determined to a resolution of 3.5 Å or better; (b) determining the three dimensional structure of the crystallized polypeptide or fragment using x-ray diffraction; and (c) identifying a druggable region of a polypeptide of the invention based on the three-dimensional structure of the polypeptide or fragment.

A three dimensional structure of a molecule or complex may be described by the set of atoms that best predict the observed diffraction data (that is, which possesses a minimal R value). Files may be created for the structure that defines each atom by its chemical identity, spatial coordinates in three dimensions, root mean squared deviation from the mean observed position and fractional occupancy of the observed position.

Those of skill in the art understand that a set of structure coordinates for an protein, complex or a portion thereof, is a relative set of points that define a shape in three dimensions. Thus, it is possible that an entirely different set of coordinates could define a similar or identical shape. Moreover, slight variations in the individual coordinates may have little affect on overall shape. Such variations in coordinates may be generated because of mathematical manipulations of the structure coordinates. For example, structure coordinates could be manipulated by crystallographic permutations of the structure coordinates, fractionalization of the structure coordinates, integer additions or subtractions to sets of the structure coordinates, inversion of the structure coordinates or any combination of the above. Alternatively, modifications in the crystal structure due to mutations, additions, substitutions, and/or deletions of amino acids, or other changes in any of the components that make up the crystal, could also yield variations in structure coordinates. Such slight variations in the individual coordinates will have little affect on overall shape. If such variations are within an acceptable standard error as compared to the original coordinates, the resulting three-dimensional shape is considered to be structurally equivalent. It should be noted that slight variations in individual structure coordinates of a polypeptide of the invention or a complex thereof would not be expected to significantly alter the nature of modulators that could associate with a druggable region thereof. Thus, for example, a modulator that bound to the active site of a polypeptide of the invention would also be expected to bind to or interfere with another active site whose structure coordinates define a shape that falls within the acceptable error.

A crystal structure of the present invention may be used to make a structural or computer model of the polypeptide, complex or portion thereof. A model may represent the secondary, tertiary and/or quaternary structure of the polypeptide, complex or portion. The configurations of points in space derived from structure coordinates according to the invention can be visualized as, for example, a holographic image, a stereodiagram, a model or a computer-displayed image, and the invention thus includes such images, diagrams or models.

(iii) Structural Equivalents

Various computational analyses can be used to determine whether a molecule or the active site portion thereof is structurally equivalent with respect to its three-dimensional structure, to all or part of a structure of a polypeptide of the invention or a portion thereof.

For the purpose of this invention, any molecule or complex or portion thereof, that has a root mean square deviation of conserved residue backbone atoms (N, Cα, C, O) of less than about 1.75 Å, when superimposed on the relevant backbone atoms described by the reference structure coordinates of a polypeptide of the invention, is considered "structurally equivalent" to the reference molecule. That is to say, the crystal structures of those portions of the two molecules are substantially identical, within acceptable error. Alternatively, the root mean square deviation may be is less than about 1.50, 1.40, 1.25, 1.0, 0.75, 0.5 or 0.35 Å.

The term "root mean square deviation" is understood in the art and means the square root of the arithmetic mean of the squares of the deviations. It is a way to express the deviation or variation from a trend or object.

In another aspect, the present invention provides a scalable three-dimensional configuration of points, at least a portion of said points, and preferably all of said points, derived from structural coordinates of at least a portion of a polypeptide of the invention and having a root mean square deviation from the structure coordinates of the polypeptide of the invention of less than 1.50, 1.40, 1.25, 1.0, 0.75, 0.5 or 0.35 Å. In certain embodiments, the portion of a polypeptide of the invention is 25%, 33%, 50%, 66%, 75%, 85%, 90% or 95% or more of the amino acid residues contained in the polypeptide.

In another aspect, the present invention provides a molecule or complex including a druggable region of a polypeptide of the invention, the druggable region being defined by a set of points having a root mean square deviation of less than about 1.75 Å from the structural coordinates for points representing (a) the backbone atoms of the amino acids

contained in a druggable region of a polypeptide of the invention, (b) the side chain atoms (and optionally the Cα atoms) of the amino acids contained in such druggable region, or (c) all the atoms of the amino acids contained in such druggable region. In certain embodiments, only a portion of the amino acids of a druggable region may be included in the set of points, such as 25%, 33%, 50%, 66%, 75%, 85%, 90% or 95% or more of the amino acid residues contained in the druggable region. In certain embodiments, the root mean square deviation may be less than 1.50, 1.40, 1.25, 1.0, 0.75, 0.5, or 0.35 Å. In still other embodiments, instead of a druggable region, a stable domain, fragment or structural motif is used in place of a druggable region.

(iv) Machine Displays and Machine Readable Storage Media

The invention provides a machine-readable storage medium including a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, displays a graphical three-dimensional representation of any of the molecules or complexes, or portions thereof, of this invention. In another embodiment, the graphical three-dimensional representation of such molecule, complex or portion thereof includes the root mean square deviation of certain atoms of such molecule by a specified amount, such as the backbone atoms by less than 0.8 Å. In another embodiment, a structural equivalent of such molecule, complex, or portion thereof, may be displayed. In another embodiment, the portion may include a druggable region of the polypeptide of the invention.

According to one embodiment, the invention provides a computer for determining at least a portion of the structure coordinates corresponding to x-ray diffraction data obtained from a molecule or complex, wherein said computer includes: (a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises at least a portion of the structural coordinates of a polypeptide of the invention; (b) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises x-ray diffraction data from said molecule or complex; (c) a working memory for storing instructions for processing said machine-readable data of (a) and (b); (d) a central-processing unit coupled to said working memory and to said machine-readable data storage medium of (a) and (b) for performing a Fourier transform of the machine readable data of (a) and for processing said machine readable data of (b) into structure coordinates; and (e) a display coupled to said central-processing unit for displaying said structure coordinates of said molecule or

complex. In certain embodiments, the structural coordinates displayed are structurally equivalent to the structural coordinates of a polypeptide of the invention.

In an alternative embodiment, the machine-readable data storage medium includes a data storage material encoded with a first set of machine readable data which includes the Fourier transform of the structure coordinates of a polypeptide of the invention or a portion thereof, and which, when using a machine programmed with instructions for using said data, can be combined with a second set of machine readable data including the x-ray diffraction pattern of a molecule or complex to determine at least a portion of the structure coordinates corresponding to the second set of machine readable data.

For example, a system for reading a data storage medium may include a computer including a central processing unit ("CPU"), a working memory which may be, e.g., RAM (random access memory) or "core" memory, mass storage memory (such as one or more disk drives or CD-ROM drives), one or more display devices (e.g., cathode-ray tube ("CRT") displays, light emitting diode ("LED") displays, liquid crystal displays ("LCDs"), electroluminescent displays, vacuum fluorescent displays, field emission displays ("FEDs"), plasma displays, projection panels, etc.), one or more user input devices (e.g., keyboards, microphones, mice, touch screens, etc.), one or more input lines, and one or more output lines, all of which are interconnected by a conventional bidirectional system bus. The system may be a stand-alone computer, or may be networked (e.g., through local area networks, wide area networks, intranets, extranets, or the internet) to other systems (e.g., computers, hosts, servers, etc.). The system may also include additional computer controlled devices such as consumer electronics and appliances.

Input hardware may be coupled to the computer by input lines and may be implemented in a variety of ways. Machine-readable data of this invention may be inputted via the use of a modem or modems connected by a telephone line or dedicated data line. Alternatively or additionally, the input hardware may include CD-ROM drives or disk drives. In conjunction with a display terminal, a keyboard may also be used as an input device.

Output hardware may be coupled to the computer by output lines and may similarly be implemented by conventional devices. By way of example, the output hardware may include a display device for displaying a graphical representation of an active site of this invention using a program such as QUANTA as described herein. Output hardware might

also include a printer, so that hard copy output may be produced, or a disk drive, to store system output for later use.

In operation, a CPU coordinates the use of the various input and output devices, coordinates data accesses from mass storage devices, accesses to and from working memory, and determines the sequence of data processing steps. A number of programs may be used to process the machine-readable data of this invention. Such programs are discussed in reference to the computational methods of drug discovery as described herein. References to components of the hardware system are included as appropriate throughout the following description of the data storage medium.

Machine-readable storage devices useful in the present invention include, but are not limited to, magnetic devices, electrical devices, optical devices, and combinations thereof. Examples of such data storage devices include, but are not limited to, hard disk devices, CD devices, digital video disk devices, floppy disk devices, removable hard disk devices, magneto-optic disk devices, magnetic tape devices, flash memory devices, bubble memory devices, holographic storage devices, and any other mass storage peripheral device. It should be understood that these storage devices include necessary hardware (e.g., drives, controllers, power supplies, etc.) as well as any necessary media (e.g., disks, flash cards, etc.) to enable the storage of data.

In one embodiment, the present invention contemplates a computer readable storage medium comprising structural data, wherein the data include the identity and three-dimensional coordinates of a polypeptide of the invention or portion thereof. In another aspect, the present invention contemplates a database comprising the identity and three-dimensional coordinates of a polypeptide of the invention or a portion thereof. Alternatively, the present invention contemplates a database comprising a portion or all of the atomic coordinates of a polypeptide of the invention or portion thereof.

(v) Structurally Similar Molecules and Complexes

Structural coordinates for a polypeptide of the invention can be used to aid in obtaining structural information about another molecule or complex. This method of the invention allows determination of at least a portion of the three-dimensional structure of molecules or molecular complexes which contain one or more structural features that are similar to structural features of a polypeptide of the invention. Similar structural features can include, for example, regions of amino acid identity, conserved active site or binding site motifs, and similarly arranged secondary structural elements (e.g., α helices and β

sheets). Many of the methods described above for determining the structure of a polypeptide of the invention may be used for this purpose as well.

For the present invention, a "structural homolog" is a polypeptide that contains one or more amino acid substitutions, deletions, additions, or rearrangements with respect to the amino acid sequence of SEQ ID NO: 4 or other polypeptide of the invention, but that, when folded into its native conformation, exhibits or is reasonably expected to exhibit at least a portion of the tertiary (three-dimensional) structure of the polypeptide encoded by SEQ ID NO: 4 or such other polypeptide of the invention. For example, structurally homologous molecules can contain deletions or additions of one or more contiguous or noncontiguous amino acids, such as a loop or a domain. Structurally homologous molecules also include modified polypeptide molecules that have been chemically or enzymatically derivatized at one or more constituent amino acids, including side chain modifications, backbone modifications, and N- and C-terminal modifications including acetylation, hydroxylation, methylation, amidation, and the attachment of carbohydrate or lipid moieties, cofactors, and the like.

By using molecular replacement, all or part of the structure coordinates of a polypeptide of the invention can be used to determine the structure of a crystallized molecule or complex whose structure is unknown more quickly and efficiently than attempting to determine such information *ab initio*. For example, in one embodiment this invention provides a method of utilizing molecular replacement to obtain structural information about a molecule or complex whose structure is unknown including: (a) crystallizing the molecule or complex of unknown structure; (b) generating an x-ray diffraction pattern from said crystallized molecule or complex; and (c) applying at least a portion of the structure coordinates for a polypeptide of the invention to the x-ray diffraction pattern to generate a three-dimensional electron density map of the molecule or complex whose structure is unknown.

In another aspect, the present invention provides a method for generating a preliminary model of a molecule or complex whose structure coordinates are unknown, by orienting and positioning the relevant portion of a polypeptide of the invention within the unit cell of the crystal of the unknown molecule or complex so as best to account for the observed x-ray diffraction pattern of the crystal of the molecule or complex whose structure is unknown.

Structural information about a portion of any crystallized molecule or complex that is sufficiently structurally similar to a portion of a polypeptide of the invention may be resolved by this method. In addition to a molecule that shares one or more structural features with a polypeptide of the invention, a molecule that has similar bioactivity, such as the same catalytic activity, substrate specificity or ligand binding activity as a polypeptide of the invention, may also be sufficiently structurally similar to a polypeptide of the invention to permit use of the structure coordinates for a polypeptide of the invention to solve its crystal structure.

In another aspect, the method of molecular replacement is utilized to obtain structural information about a complex containing a polypeptide of the invention, such as a complex between a modulator and a polypeptide of the invention (or a domain, fragment, ortholog, homolog etc. thereof). In certain instances, the complex includes a polypeptide of the invention (or a domain, fragment, ortholog, homolog etc. thereof) co-complexed with a modulator. For example, in one embodiment, the present invention contemplates a method for making a crystallized complex comprising a polypeptide of the invention, or a fragment thereof, and a compound having a molecular weight of less than 5 kDa, the method comprising: (a) crystallizing a polypeptide of the invention such that the crystals will diffract x-rays to a resolution of 3.5 Å or better; and (b) soaking the crystal in a solution comprising the compound having a molecular weight of less than 5 kDa, thereby producing a crystallized complex comprising the polypeptide and the compound.

Using homology modeling, a computer model of a structural homolog or other polypeptide can be built or refined without crystallizing the molecule. For example, in another aspect, the present invention provides a computer-assisted method for homology modeling a structural homolog of a polypeptide of the invention including: aligning the amino acid sequence of a known or suspected structural homolog with the amino acid sequence of a polypeptide of the invention and incorporating the sequence of the homolog into a model of a polypeptide of the invention derived from atomic structure coordinates to yield a preliminary model of the homolog; subjecting the preliminary model to energy minimization to yield an energy minimized model; remodeling regions of the energy minimized model where stereochemistry restraints are violated to yield a final model of the homolog.

In another embodiment, the present invention contemplates a method for determining the crystal structure of a homolog of a polypeptide having SEQ ID NO: 2 or

SEQ ID NO: 4, or equivalent thereof, the method comprising: (a) providing the three dimensional structure of a crystallized polypeptide having SEQ ID NO: 2 or SEQ ID NO: 4, or a fragment thereof; (b) obtaining crystals of a homologous polypeptide comprising an amino acid sequence that is at least 80% identical to the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4 such that the three dimensional structure of the crystallized homologous polypeptide may be determined to a resolution of 3.5 Å or better; and (c) determining the three dimensional structure of the crystallized homologous polypeptide by x-ray crystallography based on the atomic coordinates of the three dimensional structure provided in step (a). In certain instances of the foregoing method, the atomic coordinates for the homologous polypeptide have a root mean square deviation from the backbone atoms of the polypeptide having SEQ ID NO: 2 or SEQ ID NO: 4, or a fragment thereof, of not more than 1.5 Å for all backbone atoms shared in common with the homologous polypeptide and the polypeptide having SEQ ID NO: 2 or SEQ ID NO: 4, or a fragment thereof.

(vi) NMR Analysis Using X-ray Structural Data

In another aspect, the structural coordinates of a known crystal structure may be applied to nuclear magnetic resonance data to determine the three dimensional structures of polypeptides with uncharacterized or incompletely characterized structure. (See for example, Wuthrich, 1986, John Wiley and Sons, New York: 176-199; Pflugrath et al., 1986, J. Molecular Biology 189: 383-386; Kline et al., 1986 J. Molecular Biology 189:377-382). While the secondary structure of a polypeptide may often be determined by NMR data, the spatial connections between individual pieces of secondary structure are not as readily determined. The structural coordinates of a polypeptide defined by x-ray crystallography can guide the NMR spectroscopist to an understanding of the spatial interactions between secondary structural elements in a polypeptide of related structure. Information on spatial interactions between secondary structural elements can greatly simplify NOE data from two-dimensional NMR experiments. In addition, applying the structural coordinates after the determination of secondary structure by NMR techniques simplifies the assignment of NOE's relating to particular amino acids in the polypeptide sequence.

In an embodiment, the invention relates to a method of determining three dimensional structures of polypeptides with unknown structures, by applying the structural coordinates of a crystal of the present invention to nuclear magnetic resonance data of the unknown structure. This method comprises the steps of: (a) determining the secondary

structure of an unknown structure using NMR data; and (b) simplifying the assignment of through-space interactions of amino acids. The term "through-space interactions" defines the orientation of the secondary structural elements in the three dimensional structure and the distances between amino acids from different portions of the amino acid sequence. The term "assignment" defines a method of analyzing NMR data and identifying which amino acids give rise to signals in the NMR spectrum.

For all of this section on x-ray crystallography, see also Brooks et al. (1983) *J Comput Chem* 4:187-217; Weiner et al (1981) *J. Comput. Chem.* 106: 765; Eisenfield et al. (1991) *Am J Physiol* 261:C376-386; Lybrand (1991) *J Pharm Belg* 46:49-54; Froimowitz (1990) *Biotechniques* 8:640-644; Burbam et al. (1990) *Proteins* 7:99-111; Pedersen (1985) *Environ Health Perspect* 61:185-190; and Kini et al. (1991) *J Biomol Struct Dyn* 9:475-488; Ryckaert et al. (1977) *J Comput Phys* 23:327; Van Gunsteren et al. (1977) *Mol Phys* 34:1311; Anderson (1983) *J Comput Phys* 52:24; J. Mol. Biol. 48: 442-453, 1970; Dayhoff et al., Meth. Enzymol. 91: 524-545, 1983; Henikoff and Henikoff, Proc. Nat. Acad. Sci. USA 89: 10915-10919, 1992; J. Mol. Biol. 233: 716-738, 1993; Methods in Enzymology, Volume 276, Macromolecular crystallography, Part A, ISBN 0-12-182177-3 and Volume 277, Macromolecular crystallography, Part B, ISBN 0-12-182178-1, Eds. Charles W. Carter, Jr. and Robert M. Sweet (1997), Academic Press, San Diego; Pfuetzner, et al., J. Biol. Chem. 272: 430-434 (1997).

6. Interacting Proteins

The present invention also provides methods for isolating specific protein interactors of a polypeptide of the invention, and complexes comprising a polypeptide of the invention and one or more interacting proteins. In one aspect, the present invention contemplates an isolated protein complex comprising a polypeptide of the invention and at least one protein that interacts with the polypeptide of the invention. The protein may be naturally-occurring. The interacting protein may be of ***E. faecalis*** origin. Alternatively, the interacting protein may be of mammalian origin or human origin. Either the polypeptide of the invention or the interacting protein or both may be a fusion protein.

The present invention contemplates a method for identifying a protein capable of interacting with a polypeptide of the invention or a fragment thereof, the method comprising: (a) exposing a sample to a solid substrate coupled to a polypeptide of the invention or a fragment thereof under conditions which promote protein-protein

interactions; (b) washing the solid substrate so as to remove any polypeptides interacting non-specifically with the polypeptide or fragment; (c) eluting the polypeptides which specifically interact with the polypeptide or fragment; and (d) identifying the interacting protein. The sample may be an extract of *E. faecalis*, a mammalian cell extract, a human cell extract, a purified protein (or a fragment thereof), or a mixture of purified proteins (or fragments thereof). The interacting protein may be identified by a number of methods, including mass spectrometry or protein sequencing.

In another aspect, the present invention contemplates a method for identifying a protein capable of interacting with a polypeptide of present invention or a fragment thereof, the method comprising: (a) subjecting a sample to protein-affinity chromatography on multiple columns, the columns having a polypeptide of the invention or a fragment thereof coupled to the column matrix in varying concentrations, and eluting bound components of the extract from the columns; (b) separating the components to isolate a polypeptide capable of interacting with the polypeptide or fragment; and (c) analyzing the interacting protein by mass spectrometry to identify the interacting protein. In certain instances, the foregoing method will use polyacrylamide gel electrophoresis without SDS.

In another aspect, the present invention contemplates a method for identifying a protein capable of interacting with a polypeptide of the invention, the method comprising: (a) subjecting a cellular extract or extracellular fluid to protein-affinity chromatography on multiple columns, the columns having a polypeptide of the invention or a fragment thereof coupled to the column matrix in varying concentrations, and eluting bound components of the extract from the columns; (b) gel-separating the components to isolate an interacting protein; wherein the interacting protein is observed to vary in amount in direct relation to the concentration of coupled polypeptide or fragment; (c) digesting the interacting protein to give corresponding peptides; (d) analyzing the peptides by MALDI-TOF mass spectrometry or post source decay to determine the peptide masses; and (d) performing correlative database searches with the peptide, or peptide fragment, masses, whereby the interacting protein is identified based on the masses of the peptides or peptide fragments. The foregoing method may include the further step of including the identifies of any interacting proteins into a relational database.

In another aspect, the invention further contemplates a method for identifying modulators of a protein complex, the method comprising: (a) contacting a protein complex comprising a polypeptide of the invention and an interacting protein with one or more test

compounds; and (b) determining the effect of the test compound on (i) the activity of the protein complex, (ii) the amount of the protein complex, (iii) the stability of the protein complex, (iv) the conformation of the protein complex, (v) the activity of at least one polypeptide included in the protein complex, (vi) the conformation of at least one polypeptide included in the protein complex, (vii) the intracellular localization of the protein complex or a component thereof, (viii) the transcription level of a gene dependent on the complex, and/or (ix) the level of second messenger levels in a cell; thereby identifying modulators of the protein complex. The foregoing method may be carried out *in vitro* or *in vivo* as appropriate.

Typically, it will be desirable to immobilize a polypeptide of the invention to facilitate separation of complexes comprising a polypeptide of the invention from uncomplexed forms of the interacting proteins, as well as to accommodate automation of the assay. The polypeptide of the invention, or ligand, may be immobilized onto a solid support (e.g., column matrix, microtiter plate, slide, etc.). In certain embodiments, the ligand may be purified. In certain instances, a fusion protein may be provided which adds a domain that permits the ligand to be bound to a support.

In various *in vitro* embodiments, the set of proteins engaged in a protein-protein interaction comprises a cell extract, a clarified cell extract, or a reconstituted protein mixture of at least semi-purified proteins. By semi-purified, it is meant that the proteins utilized in the reconstituted mixture have been previously separated from other cellular or viral proteins. For instance, in contrast to cell lysates, the proteins involved in a protein-protein interaction are present in the mixture to at least about 50% purity relative to all other proteins in the mixture, and more preferably are present in greater, even 90-95%, purity. In certain embodiments of the subject method, the reconstituted protein mixture is derived by mixing highly purified proteins such that the reconstituted mixture substantially lacks other proteins (such as of cellular or viral origin) which might interfere with or otherwise alter the ability to measure activity resulting from the given protein-protein interaction.

Complex formation involving a polypeptide of the invention and another component polypeptide or a substrate polypeptide, may be detected by a variety of techniques. For instance, modulation in the formation of complexes can be quantitated using, for example, detectably labeled proteins (e.g. radiolabeled, fluorescently labeled, or enzymatically labeled), by immunoassay, or by chromatographic detection.

The present invention also provides assays for identifying molecules which are modulators of a protein-protein interaction involving a polypeptide of the invention, or are a modulator of the role of the complex comprising a polypeptide of the invention in the infectivity or pathogenicity of *E. faecalis*. In one embodiment, the assay detects agents which inhibit formation or stabilization of a protein complex comprising a polypeptide of the invention and one or more additional proteins. In another embodiment, the assay detects agents which modulate the intrinsic biological activity of a protein complex comprising a polypeptide of the invention, such as an enzymatic activity, binding to other cellular components, cellular compartmentalization, signal transduction, and the like. Such modulators may be used, for example, in the treatment of *E. faecalis* related diseases or disorders. In certain embodiments, the compound is a mechanism based inhibitor which chemically alters one member of a protein-protein interaction involving a polypeptide of the invention and which is a specific inhibitor of that member, e.g. has an inhibition constant about 10-fold, 100-fold, or 1000-fold different compared to homologous proteins.

In one embodiment, proteins that interact with a polypeptide of the invention may be isolated using immunoprecipitation. A polypeptide of the invention may be expressed in *E. faecalis*, or in a heterologous system. The cells expressing a polypeptide of the invention are then lysed under conditions which maintain protein-protein interactions, and complexes comprising a polypeptide of the invention are isolated. For example, a polypeptide of the invention may be expressed in mammalian cells, including human cells, in order to identify mammalian proteins that interact with a polypeptide of the invention and therefore may play a role in *E. faecalis* infectivity or proliferation. In one embodiment, a polypeptide of the invention is expressed in the cell type for which it is desirable to find interacting proteins. For example, a polypeptide of the invention may be expressed in *E. faecalis* in order to find *E. faecalis* derived interacting proteins.

In an alternative embodiment, a polypeptide of the invention is expressed and purified and then mixed with a potential interacting protein or mixture of proteins to identify complex formation. The potential interacting protein may be a single purified or semi-purified protein, or a mixture of proteins, including a mixture of purified or semi-purified proteins, a cell lysate, a clarified cell lysate, a semi-purified cell lysate, etc.

In certain embodiments, it may be desirable to use a tagged version of a polypeptide of the invention in order to facilitate isolation of complexes from the reaction mixture. Suitable tags for immunoprecipitation experiments include HA, myc, FLAG, HIS, GST,

protein A, protein G, etc. Immunoprecipitation from a cell lysate or other protein mixture may be carried out using an antibody specific for a polypeptide of the invention or using an antibody which recognizes a tag to which a polypeptide of the invention is fused (e.g., anti-HA, anti-myc, anti-FLAG, etc.). Antibodies specific for a variety of tags are known to the skilled artisan and are commercially available from a number of sources. In the case where a polypeptide of the invention is fused to a His, GST, or protein A/G tag, immunoprecipitation may be carried out using the appropriate affinity resin (e.g., beads functionalized with Ni, glutathione, Fc region of IgG, etc.). Test compounds which modulate a protein-protein interaction involving a polypeptide of the invention may be identified by carrying out the immunoprecipitation reaction in the presence and absence of the test agent and comparing the level and/or activity of the protein complex between the two reactions.

In another embodiment, proteins that interact with a polypeptide of the invention may be identified using affinity chromatography. Some examples of such chromatography are described in USSN 09/727,812, filed November 30, 2000, and the PCT Application filed November 30, 2001 and entitled "Methods for Systematic Identification of Protein-Protein Interactions and other Properties", which claims priority to such U.S. application.

In one aspect, for affinity chromatography using a solid support, a polypeptide of the invention or a fragment thereof may be attached by a variety of means known to those of skill in the art. For example, the polypeptide may be coupled directly (through a covalent linkage) to commercially available pre-activated resins as described in Formosa et al., Methods in Enzymology 1991, 208, 24-45; Sopta et al, J. Biol. Chem. 1985, 260, 10353-60; Archambault et al., Proc. Natl. Acad. Sci. USA 1997, 94, 14300-5. Alternatively, the polypeptide may be tethered to the solid support through high affinity binding interactions. If the polypeptide is expressed fused to a tag, such as GST, the fusion tag can be used to anchor the polypeptide to the matrix support, for example Sepharose beads containing immobilized glutathione. Solid supports that take advantage of these tags are commercially available.

In another aspect, the support to which a polypeptide may be immobilized is a soluble support, which may facilitate certain steps performed in the methods of the present invention. For example, the soluble support may be soluble in the conditions employed to create a binding interaction between a target and the polypeptide, and then used under

conditions in which it is a solid for elution of the proteins or other biological materials that bind to a polypeptide.

The concentration of the coupled polypeptide may have an affect on the sensitivity of the method. In certain embodiments, to detect interactions most efficiently, the concentration of the polypeptide bound to the matrix should be at least 10-fold higher than the K_d of the interaction. Thus, the concentration of the polypeptide bound to the matrix should be highest for the detection of the weakest protein-protein interactions. However, if the concentration of the immobilized polypeptide is not as high as may be ideal, it may still be possible to observe protein-protein interactions of interest by, for example, increasing the concentration of the polypeptide or other moiety that interacts with the coupled polypeptide. The level of detection will of course vary with each different polypeptide, interactor, conditions of the assay, etc. In certain instances, the interacting protein binds to the polypeptide with a K_d of about 10^{-5} M to about 10^{-8} M or 10^{-10} M.

In another aspect, the coupling may be done at various ratios of the polypeptide to the resin. An upper limit of the protein : resin ratio may be determined by the isoelectric point and the ionic nature of the protein, although it may be possible to achieve higher polypeptide concentrations by use of various methods.

In certain embodiments, several concentrations of the polypeptide immobilized on a solid or soluble support may be used. One advantage of using multiple concentrations, although not a requirement, is that one may be able to obtain an estimate for the strength of the protein-protein interaction that is observed in the affinity chromatography experiment. Another advantage of using multiple concentrations is that a binding curve which has the proper shape may indicate that the interaction that is observed is biologically important rather than a spurious interaction with denatured protein.

In one example of such an embodiment, a series of columns may be prepared with varying concentrations of polypeptide (mg polypeptide/ml resin volume). The number of columns employed may be between 2 to 8, 10, 12, 15, 25 or more, each with a different concentration of attached polypeptide. Larger numbers of columns may be used if appropriate for the polypeptide being examined, and multiple columns may be used with the same concentration as any methods may require. In certain embodiments, 4 to 6 columns are prepared with varying concentrations of polypeptide. In another aspect of this embodiment, two control columns may be prepared: one that contains no polypeptide and a second that contains the highest concentration of polypeptide but is not treated with extract.

After elution of the columns and separation of the eluent components (by one of the methods described below), it may be possible to distinguish the interacting proteins (if any) from the non-specific bound proteins as follows. The concentration of the interacting proteins, as determined by the intensity of the band on the gel, will increase proportionally to the increase in polypeptide concentration but will be missing from the second control column. This allows for the identification of unknown interacting proteins.

The method of the invention may be used for small-scale analysis. A variety of column sizes, types, and geometries may be used. In addition, other vessel shapes and sizes having a smaller scale than is usually found in laboratory experiments may be used as well, including a plurality of wells in a plate. For high throughput analysis, it is advantageous to use small volumes, from about 20, 30, 50, 80 or 100 µl. Larger or small volumes may be used, as necessary, and it may be possible to achieve high throughput analysis using them. The entire affinity chromatography procedure may be automated by assembling the micro-columns into an array (e.g. with 96 micro-column arrays).

A variety of materials may be used as the source of potential interacting proteins. In one embodiment, a cellular extract or extracellular fluid may be used. The choice of starting material for the extract may be based upon the cell or tissue type or type of fluid that would be expected to contain proteins that interact with the target protein. Micro-organisms or other organisms are grown in a medium that is appropriate for that organism and can be grown in specific conditions to promote the expression of proteins that may interact with the target protein. Exemplary starting material that may be used to make a suitable extract are: 1) one or more types of tissue derived from an animal, plant, or other multi-cellular organism, 2) cells grown in tissue culture that were derived from an animal or human, plant or other source, 3) micro-organisms grown in suspension or non-suspension cultures, 4) virus-infected cells, 5) purified organelles (including, but not restricted to nuclei, mitochondria, membranes, Golgi, endoplasmic reticulum, lysosomes, or peroxisomes) prepared by differential centrifugation or another procedure from animal, plant or other kinds of eukaryotic cells, 6) serum or other bodily fluids including, but not limited to, blood, urine, semen, synovial fluid, cerebrospinal fluid, amniotic fluid, lymphatic fluid or interstitial fluid. In other embodiments, a total cell extract may not be the optimal source of interacting proteins. For example, if the ligand is known to act in the nucleus, a nuclear extract can provide a 10-fold enrichment of proteins that are likely to interact with the ligand. In addition, proteins that are present in the extract in low

concentrations may be enriched using another chromatographic method to fractionate the extract before screening various pools for an interacting protein.

Extracts are prepared by methods known to those of skill in the art. The extracts may be prepared at a low temperature (e.g., 4°C) in order to retard denaturation or degradation of proteins in the extract. The pH of the extract may be adjusted to be appropriate for the body fluid or tissue, cellular, or organellar source that is used for the procedure (e.g. pH 7-8 for cytosolic extracts from mammals, but low pH for lysosomal extracts). The concentration of chaotropic or non-chaotropic salts in the extracting solution may be adjusted so as to extract the appropriate sets of proteins for the procedure. Glycerol may be added to the extract, as it aids in maintaining the stability of many proteins and also reduces background non-specific binding. Both the lysis buffer and column buffer may contain protease inhibitors to minimize proteolytic degradation of proteins in the extract and to protect the polypeptide. Appropriate co-factors that could potentially interact with the interacting proteins may be added to the extracting solution. One or more nucleases or another reagent may be added to the extract, if appropriate, to prevent protein-protein interactions that are mediated by nucleic acids. Appropriate detergents or other agents may be added to the solution, if desired, to extract membrane proteins from the cells or tissue. A reducing agent (e.g. dithiothreitol or 2-mercaptoethanol or glutathione or other agent) may be added. Trace metals or a chelating agent may be added, if desired, to the extracting solution.

Usually, the extract is centrifuged in a centrifuge or ultracentrifuge or filtered to provide a clarified supernatant solution. This supernatant solution may be dialyzed using dialysis tubing, or another kind of device that is standard in the art, against a solution that is similar to, but may not be identical with, the solution that was used to make the extract. The extract is clarified by centrifugation or filtration again immediately prior to its use in affinity chromatography.

In some cases, the crude lysate will contain small molecules that can interfere with the affinity chromatography. This can be remedied by precipitating proteins with ammonium sulfate, centrifugation of the precipitate, and re-suspending the proteins in the affinity column buffer followed by dialysis. An additional centrifugation of the sample may be needed to remove any particulate matter prior to application to the affinity columns.

The amount of cell extract applied to the column may be important for any embodiment. If too little extract is applied to the column and the interacting protein is

present at low concentration, the level of interacting protein retained by the column may be difficult to detect. Conversely, if too much extract is applied to the column, protein may precipitate on the column or competition by abundant interacting proteins for the limited amount of protein ligand may result in a difficulty in detecting minor species.

The columns functionalized with a polypeptide of the invention are loaded with protein extract from an appropriate source that has been dialyzed against a buffer that is consistent with the nature of the expected interaction. The pH, salt concentrations and the presence or absence of reducing and chelating agents, trace metals, detergents, and co-factors may be adjusted according to the nature of the expected interaction. Most commonly, the pH and the ionic strength are chosen so as to be close to physiological for the source of the extract. The extract is most commonly loaded under gravity onto the columns at a flow rate of about 4-6 column volumes per hour, but this flow rate can be adjusted for particular circumstances in an automated procedure.

The volume of the extract that is loaded on the columns can be varied but is most commonly equivalent to about 5 to 10 column volumes. When large volumes of extract are loaded on the columns, there is often an improvement in the signal-to-noise ratio because more protein from the extract is available to bind to the protein ligand, whereas the background binding of proteins from the extract to the solid support saturates with low amounts of extract.

A control column may be included that contains the highest concentration of protein ligand, but buffer rather than extract is loaded onto this column. The elutions (eluates) from this column will contain polypeptide that failed to be attached to the column in a covalent manner, but no proteins that are derived from the extract.

The columns may be washed with a buffer appropriate to the nature of the interaction being analyzed, usually, but not necessarily, the same as the loading buffer. An elution buffer with an appropriate pH, glycerol, and the presence or absence of reducing agent, chelating agent, cofactors, and detergents are all important considerations. The columns may be washed with anywhere from about 5 to 20 column volumes of each wash buffer to eliminate unbound proteins from the natural extract. The flow rate of the wash is usually adjusted to about 4 to 6 column volumes per hour by using gravity or an automated procedure, but other flow rates are possible in specific circumstances.

In order to elute the proteins that have been retained by the column, the interactions between the extract proteins and the column ligand should be disrupted. This is performed

by eluting the column with a solution of salt or detergent. Retention of activity by the eluted proteins may require the presence of glycerol and a buffer of appropriate pH, as well as proper choices of ionic strength and the presence or absence of appropriate reducing agent, chelating agent, trace metals, cofactors, detergents, chaotropic agents, and other reagents. If physical identification of the bound proteins is the objective, the elution may be performed sequentially, first with buffer of high ionic strength and then with buffer containing a protein denaturant, most commonly, but not restricted to sodium dodecyl sulfate (SDS), urea, or guanidine hydrochloride. In certain instances, the column is eluted with a protein denaturant, particularly SDS, for example as a 1% SDS solution. Using only the SDS wash, and omitting the salt wash, may result in SDS-gels that have higher resolution (sharper bands with less smearing). Also, using only the SDS wash results in half as many samples to analyze. The volume of the eluting solution may be varied but is normally about 2 to 4 column volumes. For 20 ml columns, the flow rate of the eluting procedures are most commonly about 4 to 6 column volumes per hour, under gravity, but can be varied in an automated procedure.

The proteins from the extract that were bound to and are eluted from the affinity columns may be most easily resolved for identification by an electrophoresis procedure, but this procedure may be modified, replaced by another suitable method, or omitted. Any of the denaturing or non-denaturing electrophoresis procedures that are standard in the art may be used for this purpose, including SDS-PAGE, gradient gels, capillary electrophoresis, and two-dimensional gels with isoelectric focusing in the first dimension and SDS-PAGE in the second. Typically, the individual components in the column eluent are separated by polyacrylamide gel electrophoresis.

After electrophoresis, protein bands or spots may be visualized using any number of methods know to those of skill in the art, including staining techniques such as Coomassie blue or silver staining, or some other agent that is standard in the art. Alternatively, autoradiography can be used for visualizing proteins isolated from organisms cultured on media containing a radioactive label, for example $^{35}SO_4^{2-}$ or ^{35}[S]methionine, that is incorporated into the proteins. The use of radioactively labeled extract allows a distinction to be made between extract proteins that were retained by the column and proteolytic fragments of the ligand that may be released from the column.

Protein bands that are derived from the extract (i.e. it did not elute from the control column that was not loaded with protein from the extract) and bound to an experimental

column that contained polypeptide covalently attached to the solid support, and did not bind to a control column that did not contain any polypeptide, may be excised from the stained electrophoretic gel and further characterized.

To identify the protein interactor by mass spectrometry, it may be desirable to reduce the disulfide bonds of the protein followed by alkylation of the free thiols prior to digestion of the protein with protease. The reduction may be performed by treatment of the gel slice with a reducing agent, for example with dithiothreitol, whereupon, the protein is alkylated by treating the gel slice with a suitable alkylating agent, for example iodoacetamide.

Prior to analysis by mass spectrometry, the protein may be chemically or enzymatically digested. The protein sample in the gel slice may be subjected to *in-gel* digestion. Shevchenko A. et al., Mass Spectrometric Sequencing of Proteins from Silver Stained Polyacrylamide Gels. Analytical Chemistry 1996, 58, 850-858. One method of digestion is by treatment with the enzyme trypsin. The resulting peptides are extracted from the gel slice into a buffer.

The peptide fragments may be purified, for example by use of chromatography. A solid support that differentially binds the peptides and not the other compounds derived from the gel slice, the protease reaction or the peptide extract may be used. The peptides may be eluted from the solid support into a small volume of a solution that is compatible with mass spectrometry (e.g. 50% acetonitrile/0.1% trifluoroacetic acid).

The preparation of a protein sample from a gel slice that is suitable for mass spectrometry may also be done by an automated procedure.

Peptide samples derived from gel slices may be analyzed by any one of a variety of techniques in mass spectrometry as further described above. This technique may be used to assign function to an unknown protein based upon the known function of the interacting protein in the same or a homologous/orthologous organism.

Eluates from the affinity chromatography columns may also be analyzed directly without resolution by electrophoretic methods, by proteolytic digestion with a protease in solution, followed by applying the proteolytic digestion products to a reverse phase column and eluting the peptides from the column.

In yet another embodiment, proteins that interact with a polypeptide of the invention may be identified using an interaction trap assay (see also, U.S. Patent NO: 5,283,317; Zervos *et al.* (1993) *Cell* 72:223-232; Madura *et al.* (1993) *J Biol Chem* 268:12046-12054;

Bartel *et al.* (1993) *Biotechniques* 14:920-924; and Iwabuchi *et al.* (1993) *Oncogene* 8:1693-1696).

In another embodiment, a method of the present invention makes use of chimeric genes which express hybrid proteins. To illustrate, a first hybrid gene comprises the coding sequence for a DNA-binding domain of a transcriptional activator fused in frame to the coding sequence for a "bait" protein, e.g., a polypeptide of the invention of sufficient length to bind to a potential interacting protein. The second hybrid protein encodes a transcriptional activation domain fused in frame to a gene encoding a "fish" protein, e.g., a potential interacting protein of sufficient length to interact with a polypeptide of the invention portion of the bait fusion protein. If the bait and fish proteins are able to interact, e.g., form a protein-protein interaction, they bring into close proximity the two domains of the transcriptional activator. This proximity causes transcription of a reporter gene which is operably linked to a transcriptional regulatory site responsive to the transcriptional activator, and expression of the reporter gene can be detected and used to score for the interaction of the bait and fish proteins.

In accordance with the present invention, the method includes providing a host cell, typically a yeast cell, e.g., *Kluyverei lactis, Schizosaccharomyces pombe, Ustilago maydis, Saccharomyces cerevisiae, Neurospora crassa, Aspergillus niger, Aspergillus nidulans, Pichia pastoris, Candida tropicalis, and Hansenula polymorpha,* though most preferably *S cerevisiae* or *S. pombe*. The host cell contains a reporter gene having a binding site for the DNA-binding domain of a transcriptional activator used in the bait protein, such that the reporter gene expresses a detectable gene product when the gene is transcriptionally activated. The first chimeric gene may be present in a chromosome of the host cell, or as part of an expression vector.

The host cell also contains a first chimeric gene which is capable of being expressed in the host cell. The gene encodes a chimeric protein, which comprises (a) a DNA-binding domain that recognizes the responsive element on the reporter gene in the host cell, and (b) a bait protein (e.g., a polypeptide of the invention).

A second chimeric gene is also provided which is capable of being expressed in the host cell, and encodes the "fish" fusion protein. In one embodiment, both the first and the second chimeric genes are introduced into the host cell in the form of plasmids. Preferably, however, the first chimeric gene is present in a chromosome of the host cell and the second chimeric gene is introduced into the host cell as part of a plasmid.

The DNA-binding domain of the first hybrid protein and the transcriptional activation domain of the second hybrid protein may be derived from transcriptional activators having separable DNA-binding and transcriptional activation domains. For instance, these separate DNA-binding and transcriptional activation domains are known to be found in the yeast GAL4 protein, and are known to be found in the yeast GCN4 and ADR1 proteins. Many other proteins involved in transcription also have separable binding and transcriptional activation domains which make them useful for the present invention, and include, for example, the LexA and VP16 proteins. It will be understood that other (substantially) transcriptionally-inert DNA-binding domains may be used in the subject constructs; such as domains of ACE1, λcI, lac repressor, jun or fos. In another embodiment, the DNA-binding domain and the transcriptional activation domain may be from different proteins. The use of a LexA DNA binding domain provides certain advantages. For example, in yeast, the LexA moiety contains no activation function and has no known affect on transcription of yeast genes. In addition, use of LexA allows control over the sensitivity of the assay to the level of interaction (see, for example, the Brent *et al.* PCT publication WO94/10300).

In certain embodiments, any enzymatic activity associated with the bait or fish proteins is inactivated, e.g., dominant negative or other mutants of a protein-protein interaction component can be used.

Continuing with the illustrative example, a polypeptide of the invention-mediated interaction, if any, between the bait and fish fusion proteins in the host cell, causes the activation domain to activate transcription of the reporter gene. The method is carried out by introducing the first chimeric gene and the second chimeric gene into the host cell, and subjecting that cell to conditions under which the bait and fish fusion proteins and are expressed in sufficient quantity for the reporter gene to be activated. The formation of a protein complex containing a polypeptide of the invention results in a detectable signal produced by the expression of the reporter gene.

In still further embodiments, the protein-protein interaction of interest is generated in whole cells, taking advantage of cell culture techniques to support the subject assay. For example, the protein-protein interaction of interest can be constituted in a prokaryotic or eukaryotic cell culture system. Advantages to generating the protein complex in an intact cell includes the ability to screen for inhibitors of the level or activity of the complex which are functional in an environment more closely approximating that which therapeutic use of

the inhibitor would require, including the ability of the agent to gain entry into the cell. Furthermore, certain of the *in vivo* embodiments of the assay are amenable to high through-put analysis of candidate agents.

The components of the protein complex comprising a polypeptide of the invention can be endogenous to the cell selected to support the assay. Alternatively, some or all of the components can be derived from exogenous sources. For instance, fusion proteins can be introduced into the cell by recombinant techniques (such as through the use of an expression vector), as well as by microinjecting the fusion protein itself or mRNA encoding the fusion protein. Moreover, in the whole cell embodiments of the subject assay, the reporter gene construct can provide, upon expression, a selectable marker. Such embodiments of the subject assay are particularly amenable to high through-put analysis in that proliferation of the cell can provide a simple measure of the protein-protein interaction.

The amount of transcription from the reporter gene may be measured using any method known to those of skill in the art to be suitable. For example, specific mRNA expression may be detected using Northern blots or specific protein product may be identified by a characteristic stain, western blots or an intrinsic activity. In certain embodiments, the product of the reporter gene is detected by an intrinsic activity associated with that product. For instance, the reporter gene may encode a gene product that, by enzymatic activity, gives rise to a detection signal based on color, fluorescence, or luminescence.

The interaction trap assay of the invention may also be used to identify test agents capable of modulating formation of a complex comprising a polypeptide of the invention. In general, the amount of expression from the reporter gene in the presence of the test compound is compared to the amount of expression in the same cell in the absence of the test compound. Alternatively, the amount of expression from the reporter gene in the presence of the test compound may be compared with the amount of transcription in a substantially identical cell that lacks a component of the protein-protein interaction involving a polypeptide of the invention.

7. Antibodies

Another aspect of the invention pertains to antibodies specifically reactive with a polypeptide of the invention. For example, by using peptides based on a polypeptide of the invention, e.g., having an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 or an

immunogenic fragment thereof, antisera or monoclonal antibodies may be made using standard methods. An exemplary immunogenic fragment may contain eight, ten or more consecutive amino acid residues of SEQ ID NO: 2 or SEQ ID NO: 4. Certain fragments that are predicted to be immunogenic for the subject amino acid sequences (predicted) are set forth in Table 2 contained in FIGURE 7

The term "antibody" as used herein is intended to include fragments thereof which are also specifically reactive with a polypeptide of the invention. Antibodies can be fragmented using conventional techniques and the fragments screened for utility in the same manner as is suitable for whole antibodies. For example, $F(ab')_2$ fragments can be generated by treating antibody with pepsin. The resulting $F(ab')_2$ fragment can be treated to reduce disulfide bridges to produce Fab' fragments. The antibody of the present invention is further intended to include bispecific and chimeric molecules, as well as single chain (scFv) antibodies. Also within the scope of the invention are trimeric antibodies, humanized antibodies, human antibodies, and single chain antibodies. All of these modified forms of antibodies as well as fragments of antibodies are intended to be included in the term "antibody".

In one aspect, the present invention contemplates a purified antibody that binds specifically to a polypeptide of the invention and which does not substantially cross-react with a protein which is less than about 80%, or less than about 90%, identical to SEQ ID NO: 2 or SEQ ID NO: 4. In another aspect, the present invention contemplates an array comprising a substrate having a plurality of address, wherein at least one of the addresses has disposed thereon a purified antibody that binds specifically to a polypeptide of the invention.

Antibodies may be elicited by methods known in the art. For example, a mammal such as a mouse, a hamster or rabbit may be immunized with an immunogenic form of a polypeptide of the invention (e.g., an antigenic fragment which is capable of eliciting an antibody response). Alternatively, immunization may occur by using a nucleic acid of the acid, which presumably *in vivo* expresses the polypeptide of the invention giving rise to the immunogenic response observed. Techniques for conferring immunogenicity on a protein or peptide include conjugation to carriers or other techniques well known in the art. For instance, a peptidyl portion of a polypeptide of the invention may be administered in the presence of adjuvant. The progress of immunization may be monitored by detection of

antibody titers in plasma or serum. Standard ELISA or other immunoassays may be used with the immunogen as antigen to assess the levels of antibodies.

Following immunization, antisera reactive with a polypeptide of the invention may be obtained and, if desired, polyclonal antibodies isolated from the serum. To produce monoclonal antibodies, antibody producing cells (lymphocytes) may be harvested from an immunized animal and fused by standard somatic cell fusion procedures with immortalizing cells such as myeloma cells to yield hybridoma cells. Such techniques are well known in the art, and include, for example, the hybridoma technique (originally developed by Kohler and Milstein, (1975) *Nature*, 256: 495-497), as the human B cell hybridoma technique (Kozbar et al., (1983) *Immunology Today*, 4: 72), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole et al., (1985) *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc. pp. 77-96). Hybridoma cells can be screened immunochemically for production of antibodies specifically reactive with the polypeptides of the invention and the monoclonal antibodies isolated.

Antibodies directed against the polypeptides of the invention can be used to selectively block the action of the polypeptides of the invention. Antibodies against a polypeptide of the invention may be employed to treat infections, particularly bacterial infections and diseases. For example, the present invention contemplates a method for treating a subject suffering from a *E. faecalis* related disease or disorder, comprising administering to an animal having the condition a therapeutically effective amount of a purified antibody that binds specifically to a polypeptide of the invention. In another example, the present invention contemplates a method for inhibiting SEQ ID NO: 2 or SEQ ID NO: 4 dependent growth or infectivity of *E. faecalis*, comprising contacting *E. faecalis* with a purified antibody that binds specifically to a polypeptide of the invention.

In one embodiment, antibodies reactive with a polypeptide of the invention are used in the immunological screening of cDNA libraries constructed in expression vectors, such as λgt11, λgt18-23, λZAP, and λORF8. Messenger libraries of this type, having coding sequences inserted in the correct reading frame and orientation, can produce fusion proteins. For instance, λgt11 will produce fusion proteins whose amino termini consist of ß-galactosidase amino acid sequences and whose carboxy termini consist of a foreign polypeptide. Antigenic epitopes of a polypeptide of the invention can then be detected with antibodies, as, for example, reacting nitrocellulose filters lifted from phage infected bacterial plates with an antibody specific for a polypeptide of the invention. Phage scored

by this assay can then be isolated from the infected plate. Thus, homologs of a polypeptide of the invention can be detected and cloned from other sources.

Antibodies may be employed to isolate or to identify clones expressing the polypeptides to purify the polypeptides by affinity chromatography.

In other embodiments, the polypeptides of the invention may be modified so as to increase their immunogenicity. For example, a polypeptide, such as an antigenically or immunologically equivalent derivative, may be associated, for example by conjugation, with an immunogenic carrier protein for example bovine serum albumin (BSA) or keyhole limpet haemocyanin (KLH). Alternatively a multiple antigenic peptide comprising multiple copies of the protein or polypeptide, or an antigenically or immunologically equivalent polypeptide thereof may be sufficiently antigenic to improve immunogenicity so as to obviate the use of a carrier.

In other embodiments, the antibodies of the invention, or variants thereof, are modified to make them less immunogenic when administered to a subject. For example, if the subject is human, the antibody may be "humanized"; where the complimentarity determining region(s) of the hybridoma-derived antibody has been transplanted into a human monoclonal antibody, for example as described in Jones, P. et al. (1986), Nature 321, 522-525 or Tempest et al. (1991) Biotechnology 9, 266-273. Also, transgenic mice, or other mammals, may be used to express humanized antibodies. Such humanization may be partial or complete.

The use of a nucleic acid of the invention in genetic immunization may employ a suitable delivery method such as direct injection of plasmid DNA into muscles (Wolff et al., Hum Mol Genet 1992, 1:363, Manthorpe et al., Hum. Gene Ther. 1963:4, 419), delivery of DNA complexed with specific protein carriers (Wu et al., J Biol Chem. 1989: 264,16985), coprecipitation of DNA with calcium phosphate (Benvenisty & Reshef, PNAS USA, 1986:83,9551), encapsulation of DNA in various forms of liposomes (Kaneda et al., Science 1989:243,375), particle bombardment (Tang et al., Nature 1992, 356:152, Eisenbraun et al., DNA Cell Biol 1993, 12:791) and *in vivo* infection using cloned retroviral vectors (Seeger et al., PNAS USA 1984:81,5849).

8. Diagnostic Assays

The invention further provides a method for detecting the presence of *E. faecalis* in a biological sample. Detection of *E. faecalis* in a subject, particularly a mammal, and

especially a human, will provide a diagnostic method for diagnosis of a *E. faecalis* related disease or disorder. In general, the method involves contacting the biological sample with a compound or an agent capable of detecting a polypeptide of the invention or a nucleic acid of the invention. The term "biological sample" when used in reference to a diagnostic assay is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject.

The detection method of the invention may be used to detect the presence of *E. faecalis* in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of a nucleic acid of the invention include Northern hybridizations and in situ hybridizations. *In vitro* techniques for detection of polypeptides of the invention include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, immunofluorescence, radioimmunoassays and competitive binding assays. Alternatively, polypeptides of the invention can be detected *in vivo* in a subject by introducing into the subject a labeled antibody specific for a polypeptide of the invention. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques. It may be possible to use all of the diagnostic methods disclosed herein for pathogens in addition to *E. faecalis*.

Nucleic acids for diagnosis may be obtained from an infected individual's cells and tissues, such as bone, blood, muscle, cartilage, and skin. Nucleic acids, e.g., DNA and RNA, may be used directly for detection or may be amplified, e.g., enzymatically by using PCR or other amplification technique, prior to analysis. Using amplification, characterization of the species and strain of prokaryote present in an individual, may be made by an analysis of the genotype of the prokaryote gene. Deletions and insertions can be detected by a change in size of the amplified product in comparison to the genotype of a reference sequence. Point mutations can be identified by hybridizing a nucleic acid, e.g., amplified DNA, to a nucleic acid of the invention, which nucleic acid may be labeled. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase digestion or by differences in melting temperatures. DNA sequence differences may also be detected by alterations in the electrophoretic mobility of the DNA fragments in gels, with or without denaturing agents, or by direct DNA sequencing. See, e.g. Myers et al., Science, 230: 1242 (1985). Sequence changes at specific locations also may be revealed by nuclease protection assays, such as RNase and S1 protection or a chemical cleavage method. See, e.g., Cotton et al., Proc. Natl. Acad. Sci., USA, 85: 4397-4401 (1985).

Agents for detecting a nucleic acid of the invention, e.g., comprising the sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 3, include labeled or labelable nucleic acid probes capable of hybridizing to a nucleic acid of the invention. The nucleic acid probe can comprise, for example, the full length sequence of a nucleic acid of the invention, or an equivalent thereof, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to SEQ ID NO: 1 or SEQ ID NO: 3, or the complement thereof. Agents for detecting a polypeptide of the invention, e.g., comprising an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4, include labeled or labelable antibodies capable of binding to a polypeptide of the invention. Antibodies may be polyclonal, or alternatively, monoclonal. An intact antibody, or a fragment thereof (e.g., Fab or $F(ab')_2$) can be used. Labeling the probe or antibody also encompasses direct labeling of the probe or antibody by coupling (e.g., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

In certain embodiments, detection of a nucleic acid of the invention in a biological sample involves the use of a probe/primer in a polymerase chain reaction (PCR) (see, e.g. U.S. Pat. Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, e.g., Landegran et al. (1988) Science 241:1077-1080; and Nakazawa et al. (1994) PNAS 91:360-364), the latter of which can be particularly useful for distinguishing between orthologs of polynucleotides of the invention (see Abravaya et al. (1995) Nucleic Acids Res. 23:675-682). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (e.g., genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a nucleic acid of the invention under conditions such that hybridization and amplification of the polynucleotide (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample.

In one aspect, the present invention contemplates a method for detecting the presence of *E. faecalis* in a sample, the method comprising: (a) providing a sample to be tested for the presence of *E. faecalis*; (b) contacting the sample with an antibody reactive

against eight consecutive amino acid residues of SEQ ID NO: 2 or SEQ ID NO: 4 under conditions which permit association between the antibody and its ligand; and (c) detecting interaction of the antibody with its ligand, thereby detecting the presence of *E. faecalis* in the sample.

In another aspect, the present invention contemplates a method for detecting the presence of *E. faecalis* in a sample, the method comprising: (a) providing a sample to be tested for the presence of *E. faecalis*; (b) contacting the sample with an antibody that binds specifically to a polypeptide of the invention under conditions which permit association between the antibody and its ligand; and (c) detecting interaction of the antibody with its ligand, thereby detecting the presence of *E. faecalis* in the sample.

In yet another example, the present invention contemplates a method for diagnosing a patient suffering from a *E. faecalis* related disease or disorder, comprising: (a) obtaining a biological sample from a patient; (b) detecting the presence or absence of a polypeptide of the invention, or a nucleic acid encoding a polypeptide of the invention, in the sample; and (c) diagnosing a patient suffering from a *E. faecalis* related disease or disorder based on the presence of a polypeptide of the invention, or a nucleic acid encoding a polypeptide of the invention, in the patient sample.

The diagnostic assays of the invention may also be used to monitor the effectiveness of an anti-*E. faecalis* treatment in an individual suffering from an *E. faecalis* related disease or disorder. For example, the presence and/or amount of a nucleic acid of the invention or a polypeptide of the invention can be detected in an individual suffering from an *E. faecalis* related disease or disorder before and after treatment with anti-*E. faecalis* therapeutic agent. Any change in the level of a polynucleotide or polypeptide of the invention after treatment of the individual with the therapeutic agent can provide information about the effectiveness of the treatment course. In particular, no change, or a decrease, in the level of a polynucleotide or polypeptide of the invention present in the biological sample will indicate that the therapeutic is successfully combating the *E. faecalis* related disease or disorder.

The invention also encompasses kits for detecting the presence of *E. faecalis* in a biological sample. For example, the kit can comprise a labeled or labelable compound or agent capable of detecting a polynucleotide or polypeptide of the invention in a biological sample; means for determining the amount of *E. faecalis* in the sample; and means for comparing the amount of *E. faecalis* in the sample with a standard. The compound or agent

can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect a polynucleotide or polypeptide of the invention.

9. Drug Discovery

Modulators to polypeptides of the invention and other structurally related molecules, and complexes containing the same, may be identified and developed as set forth below and otherwise using techniques and methods known to those of skill in the art. The modulators of the invention may be employed, for instance, to inhibit and treat *E. faecalis* associated diseases or conditions, such as urinary tract infection, surgical wound infection, bacteremia, intra abdominal infection, pelvic infection, central nervous system infection, osteomyelitis, pulmonary infection, and endocarditis.

A variety of methods for inhibiting the growth or infectivity of *E. faecalis* are contemplated by the present invention. For example, exemplary methods involve contacting *E. faecalis* with a polypeptide of the invention that modulates the same or another polypeptide from such pathogen, a nucleic acid encoding such polypeptide of the invention, or a compound thought or shown to be effective against such pathogen.

For example, in one aspect, the present invention contemplates a method for treating a patient suffering from an infection of *E. faecalis*, comprising administering to the patient an amount of a SEQ ID NO: 2 or SEQ ID NO: 4 inhibitor effective to inhibit the expression and/or activity of a polypeptide of the invention. In certain instances, the animal is a human or a livestock animal such as a cow, pig, goat or sheep. The present invention further contemplates a method for treating a subject suffering from a *E. faecalis* related disease or disorder, comprising administering to an animal having the condition a therapeutically effective amount of a molecule identified using one of the methods of the present invention.

The present invention contemplates making any molecule that is shown to modulate the activity of a polypeptide of the invention.

In another embodiment, inhibitors, modulators of the subject polypeptides, or biological complexes containing them, may be used in the manufacture of a medicament for any number of uses, including, for example, treating any disease or other treatable condition of a patient (including humans and animals), and particularly a disease caused by *E. faecalis*, such as, for example, one of the following: urinary tract infection, surgical wound infection, bacteremia, intra abdominal infection, pelvic infection, central nervous system infection, osteomyelitis, pulmonary infection, and endocarditis.

(a) Drug Design

A number of techniques can be used to screen, identify, select and design chemical entities capable of associating with polypeptides of the invention, structurally homologous molecules, and other molecules. Knowledge of the structure for a polypeptide of the invention, determined in accordance with the methods described herein, permits the design and/or identification of molecules and/or other modulators which have a shape complementary to the conformation of a polypeptide of the invention, or more particularly, a druggable region thereof. It is understood that such techniques and methods may use, in addition to the exact structural coordinates and other information for a polypeptide of the invention, structural equivalents thereof described above (including, for example, those structural coordinates that are derived from the structural coordinates of amino acids contained in a druggable region as described above).

The term "chemical entity," as used herein, refers to chemical compounds, complexes of two or more chemical compounds, and fragments of such compounds or complexes. In certain instances, it is desirable to use chemical entities exhibiting a wide range of structural and functional diversity, such as compounds exhibiting different shapes (e.g., flat aromatic rings(s), puckered aliphatic rings(s), straight and branched chain aliphatics with single, double, or triple bonds) and diverse functional groups (e.g., carboxylic acids, esters, ethers, amines, aldehydes, ketones, and various heterocyclic rings).

In one aspect, the method of drug design generally includes computationally evaluating the potential of a selected chemical entity to associate with any of the molecules or complexes of the present invention (or portions thereof). For example, this method may include the steps of (a) employing computational means to perform a fitting operation between the selected chemical entity and a druggable region of the molecule or complex; and (b) analyzing the results of said fitting operation to quantify the association between the chemical entity and the druggable region.

A chemical entity may be examined either through visual inspection or through the use of computer modeling using a docking program such as GRAM, DOCK, or AUTODOCK (Dunbrack et al., Folding & Design, 2:27-42 (1997)). This procedure can include computer fitting of chemical entities to a target to ascertain how well the shape and the chemical structure of each chemical entity will complement or interfere with the structure of the subject polypeptide (Bugg et al., Scientific American, Dec.: 92-98 (1993); West et al., TIPS, 16:67-74 (1995)). Computer programs may also be employed to estimate

the attraction, repulsion, and steric hindrance of the chemical entity to a druggable region, for example. Generally, the tighter the fit (e.g., the lower the steric hindrance, and/or the greater the attractive force) the more potent the chemical entity will be because these properties are consistent with a tighter binding constant. Furthermore, the more specificity in the design of a chemical entity the more likely that the chemical entity will not interfere with related proteins, which may minimize potential side-effects due to unwanted interactions.

A variety of computational methods for molecular design, in which the steric and electronic properties of druggable regions are used to guide the design of chemical entities, are known: Cohen et al. (1990) *J. Med. Cam.* 33: 883-894; Kuntz et al. (1982) *J. Mol. Biol* 161: 269-288; DesJarlais (1988) *J. Med. Cam.* 31: 722-729; Bartlett et al. (1989) *Spec. Publ., Roy. Soc. Chem.* 78: 182-196; Goodford et al. (1985) *J. Med. Cam.* 28: 849-857; and DesJarlais et al. *J. Med. Cam.* 29: 2149-2153. Directed methods generally fall into two categories: (1) design by analogy in which 3-D structures of known chemical entities (such as from a crystallographic database) are docked to the druggable region and scored for goodness-of-fit; and (2) *de novo* design, in which the chemical entity is constructed piece-wise in the druggable region. The chemical entity may be screened as part of a library or a database of molecules. Databases which may be used include ACD (Molecular Designs Limited), NCI (National Cancer Institute), CCDC (Cambridge Crystallographic Data Center), CAST (Chemical Abstract Service), Derwent (Derwent Information Limited), Maybridge (Maybridge Chemical Company Ltd), Aldrich (Aldrich Chemical Company), DOCK (University of California in San Francisco), and the Directory of Natural Products (Chapman & Hall). Computer programs such as CONCORD (Tripos Associates) or DB-Converter (Molecular Simulations Limited) can be used to convert a data set represented in two dimensions to one represented in three dimensions.

Chemical entities may be tested for their capacity to fit spatially with a druggable region or other portion of a target protein. As used herein, the term "fits spatially" means that the three-dimensional structure of the chemical entity is accommodated geometrically by a druggable region. A favorable geometric fit occurs when the surface area of the chemical entity is in close proximity with the surface area of the druggable region without forming unfavorable interactions. A favorable complementary interaction occurs where the chemical entity interacts by hydrophobic, aromatic, ionic, dipolar, or hydrogen donating

and accepting forces. Unfavorable interactions may be steric hindrance between atoms in the chemical entity and atoms in the druggable region.

If a model of the present invention is a computer model, the chemical entities may be positioned in a druggable region through computational docking. If, on the other hand, the model of the present invention is a structural model, the chemical entities may be positioned in the druggable region by, for example, manual docking. As used herein the term "docking" refers to a process of placing a chemical entity in close proximity with a druggable region, or a process of finding low energy conformations of a chemical entity/druggable region complex.

In an illustrative embodiment, the design of potential modulator begins from the general perspective of shape complimentary for the druggable region of a polypeptide of the invention, and a search algorithm is employed which is capable of scanning a database of small molecules of known three-dimensional structure for chemical entities which fit geometrically with the target druggable region. Most algorithms of this type provide a method for finding a wide assortment of chemical entities that are complementary to the shape of a druggable region of the subject polypeptide. Each of a set of chemical entities from a particular data-base, such as the Cambridge Crystallographic Data Bank (CCDB) (Allen et al. (1973) *J. Chem. Doc.* 13: 119), is individually docked to the druggable region of a polypeptide of the invention in a number of geometrically permissible orientations with use of a docking algorithm. In certain embodiments, a set of computer algorithms called DOCK, can be used to characterize the shape of invaginations and grooves that form the active sites and recognition surfaces of the druggable region (Kuntz et al. (1982) *J. Mol. Biol* 161: 269-288). The program can also search a database of small molecules for templates whose shapes are complementary to particular binding sites of a polypeptide of the invention (DesJarlais et al. (1988) *J Med Chem* 31: 722-729).

The orientations are evaluated for goodness-of-fit and the best are kept for further examination using molecular mechanics programs, such as AMBER or CHARMM. Such algorithms have previously proven successful in finding a variety of chemical entities that are complementary in shape to a druggable region.

Goodford (1985, *J Med Chem* 28:849-857) and Boobbyer et al. (1989, *J Med Chem* 32:1083-1094) have produced a computer program (GRID) which seeks to determine regions of high affinity for different chemical groups (termed probes) of the druggable region. GRID hence provides a tool for suggesting modifications to known chemical entities that might

enhance binding. It may be anticipated that some of the sites discerned by GRID as regions of high affinity correspond to "pharmacophoric patterns" determined inferentially from a series of known ligands. As used herein, a "pharmacophoric pattern" is a geometric arrangement of features of chemical entities that is believed to be important for binding. Attempts have been made to use pharmacophoric patterns as a search screen for novel ligands (Jakes et al. (1987) *J Mol Graph* 5:41-48; Brint et al. (1987) *J Mol Graph* 5:49-56; Jakes et al. (1986) *J Mol Graph* 4:12-20).

Yet a further embodiment of the present invention utilizes a computer algorithm such as CLIX which searches such databases as CCDB for chemical entities which can be oriented with the druggable region in a way that is both sterically acceptable and has a high likelihood of achieving favorable chemical interactions between the chemical entity and the surrounding amino acid residues. The method is based on characterizing the region in terms of an ensemble of favorable binding positions for different chemical groups and then searching for orientations of the chemical entities that cause maximum spatial coincidence of individual candidate chemical groups with members of the ensemble. The algorithmic details of CLIX is described in Lawrence et al. (1992) *Proteins* 12:31-41.

In this way, the efficiency with which a chemical entity may bind to or interfere with a druggable region may be tested and optimized by computational evaluation. For example, for a favorable association with a druggable region, a chemical entity must preferably demonstrate a relatively small difference in energy between its bound and fine states (i.e., a small deformation energy of binding). Thus, certain, more desirable chemical entities will be designed with a deformation energy of binding of not greater than about 10 kcal/mole, and more preferably, not greater than 7 kcal/mole. Chemical entities may interact with a druggable region in more than one conformation that is similar in overall binding energy. In those cases, the deformation energy of binding is taken to be the difference between the energy of the free entity and the average energy of the conformations observed when the chemical entity binds to the target.

In this way, the present invention provides computer-assisted methods for identifying or designing a potential modulator of the activity of a polypeptide of the invention including: supplying a computer modeling application with a set of structure coordinates of a molecule or complex, the molecule or complex including at least a portion of a druggable region from a polypeptide of the invention; supplying the computer modeling application with a set of structure coordinates of a chemical entity; and

determining whether the chemical entity is expected to bind to the molecule or complex, wherein binding to the molecule or complex is indicative of potential modulation of the activity of a polypeptide of the invention.

In another aspect, the present invention provides a computer-assisted method for identifying or designing a potential modulator to a polypeptide of the invention, supplying a computer modeling application with a set of structure coordinates of a molecule or complex, the molecule or complex including at least a portion of a druggable region of a polypeptide of the invention; supplying the computer modeling application with a set of structure coordinates for a chemical entity; evaluating the potential binding interactions between the chemical entity and active site of the molecule or molecular complex; structurally modifying the chemical entity to yield a set of structure coordinates for a modified chemical entity, and determining whether the modified chemical entity is expected to bind to the molecule or complex, wherein binding to the molecule or complex is indicative of potential modulation of the polypeptide of the invention.

In one embodiment, a potential modulator can be obtained by screening a peptide library (Scott and Smith, Science, 249:386-390 (1990); Cwirla et al., Proc. Natl. Acad. Sci., 87:6378-6382 (1990); Devlin et al., Science, 249:404-406 (1990)). A potential modulator selected in this manner could then be systematically modified by computer modeling programs until one or more promising potential drugs are identified. Such analysis has been shown to be effective in the development of HIV protease inhibitors (Lam et al., Science 263:380-384 (1994); Wlodawer et al., Ann. Rev. Biochem. 62:543-585 (1993); Appelt, Perspectives in Drug Discovery and Design 1:23-48 (1993); Erickson, Perspectives in Drug Discovery and Design 1:109-128 (1993)). Alternatively a potential modulator may be selected from a library of chemicals such as those that can be licensed from third parties, such as chemical and pharmaceutical companies. A third alternative is to synthesize the potential modulator *de novo*.

For example, in certain embodiments, the present invention provides a method for making a potential modulator for a polypeptide of the invention, the method including synthesizing a chemical entity or a molecule containing the chemical entity to yield a potential modulator of a polypeptide of the invention, the chemical entity having been identified during a computer-assisted process including supplying a computer modeling application with a set of structure coordinates of a molecule or complex, the molecule or complex including at least one druggable region from a polypeptide of the invention;

supplying the computer modeling application with a set of structure coordinates of a chemical entity; and determining whether the chemical entity is expected to bind to the molecule or complex at the active site, wherein binding to the molecule or complex is indicative of potential modulation. This method may further include the steps of evaluating the potential binding interactions between the chemical entity and the active site of the molecule or molecular complex and structurally modifying the chemical entity to yield a set of structure coordinates for a modified chemical entity, which steps may be repeated one or more times.

Once a potential modulator is identified, it can then be tested in any standard assay for the macromolecule depending of course on the macromolecule, including in high throughput assays. Further refinements to the structure of the modulator will generally be necessary and can be made by the successive iterations of any and/or all of the steps provided by the particular screening assay, in particular further structural analysis by e.g., ^{15}N NMR relaxation rate determinations or x-ray crystallography with the modulator bound to the subject polypeptide. These studies may be performed in conjunction with biochemical assays.

Once identified, a potential modulator may be used as a model structure, and analogs to the compound can be obtained. The analogs are then screened for their ability to bind the subject polypeptide. An analog of the potential modulator might be chosen as a modulator when it binds to the subject polypeptide with a higher binding affinity than the predecessor modulator.

In a related approach, iterative drug design is used to identify modulators of a target protein. Iterative drug design is a method for optimizing associations between a protein and a modulator by determining and evaluating the three dimensional structures of successive sets of protein/modulator complexes. In iterative drug design, crystals of a series of protein/modulator complexes are obtained and then the three-dimensional structures of each complex is solved. Such an approach provides insight into the association between the proteins and modulators of each complex. For example, this approach may be accomplished by selecting modulators with inhibitory activity, obtaining crystals of this new protein/modulator complex, solving the three dimensional structure of the complex, and comparing the associations between the new protein/modulator complex and previously solved protein/modulator complexes. By observing how changes in the modulator affected the protein/modulator associations, these associations may be optimized.

In addition to designing and/or identifying a chemical entity to associate with a druggable region, as described above, the same techniques and methods may be used to design and/or identify chemical entities that either associate, or do not associate, with affinity regions, selectivity regions or undesired regions of protein targets. By such methods, selectivity for one or a few targets, or alternatively for multiple targets, from the same species or from multiple species, can be achieved.

For example, a chemical entity may be designed and/or identified for which the binding energy for one druggable region, e.g., an affinity region or selectivity region, is more favorable than that for another region, e.g., an undesired region, by about 20%, 30%, 50% to about 60% or more. It may be the case that the difference is observed between (a) more than two regions, (b) between different regions (selectivity, affinity or undesirable) from the same target, (c) between regions of different targets, (d) between regions of homologs from different species, or (e) between other combinations. Alternatively, the comparison may be made by reference to the Kd, usually the apparent Kd, of said chemical entity with the two or more regions in question.

In another aspect, prospective modulators are screened for binding to two nearby druggable regions on a target protein. For example, a modulator that binds a first region of a target polypeptide does not bind a second nearby region. Binding to the second region can be determined by monitoring changes in a different set of amide chemical shifts in either the original screen or a second screen conducted in the presence of a modulator (or potential modulator) for the first region. From an analysis of the chemical shift changes, the approximate location of a potential modulator for the second region is identified. Optimization of the second modulator for binding to the region is then carried out by screening structurally related compounds (e.g., analogs as described above). When modulators for the first region and the second region are identified, their location and orientation in the ternary complex can be determined experimentally. On the basis of this structural information, a linked compound, e.g., a consolidated modulator, is synthesized in which the modulator for the first region and the modulator for the second region are linked. In certain embodiments, the two modulators are covalently linked to form a consolidated modulator. This consolidated modulator may be tested to determine if it has a higher binding affinity for the target than either of the two individual modulators. A consolidated modulator is selected as a modulator when it has a higher binding affinity for the target than either of the two modulators. Larger consolidated modulators can be constructed in an

analogous manner, e.g., linking three modulators which bind to three nearby regions on the target to form a multilinked consolidated modulator that has an even higher affinity for the target than the linked modulator. In this example, it is assumed that is desirable to have the modulator bind to all the druggable regions. However, it may be the case that binding to certain of the druggable regions is not desirable, so that the same techniques may be used to identify modulators and consolidated modulators that show increased specificity based on binding to at least one but not all druggable regions of a target.

The present invention provides a number of methods that use drug design as described above. For example, in one aspect, the present invention contemplates a method for designing a candidate compound for screening for inhibitors of a polypeptide of the invention, the method comprising: (a) determining the three dimensional structure of a crystallized polypeptide of the invention or a fragment thereof; and (b) designing a candidate inhibitor based on the three dimensional structure of the crystallized polypeptide or fragment.

In another aspect, the present invention contemplates a method for identifying a potential inhibitor of a polypeptide of the invention, the method comprising: (a) providing the three-dimensional coordinates of a polypeptide of the invention or a fragment thereof; (b) identifying a druggable region of the polypeptide or fragment; and (c) selecting from a database at least one compound that comprises three dimensional coordinates which indicate that the compound may bind the druggable region; (d) wherein the selected compound is a potential inhibitor of a polypeptide of the invention.

In another aspect, the present invention contemplates a method for identifying a potential modulator of a molecule comprising a druggable region similar to that of SEQ ID NO: 2 or SEQ ID NO: 4, the method comprising: (a) using the atomic coordinates of amino acid residues from SEQ ID NO: 2 or SEQ ID NO: 4, or a fragment thereof, ± a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5 Å, to generate a three-dimensional structure of a molecule comprising a druggable region that is a portion of SEQ ID NO: 2 or SEQ ID NO: 4; (b) employing the three dimensional structure to design or select the potential modulator; (c) synthesizing the modulator; and (d) contacting the modulator with the molecule to determine the ability of the modulator to interact with the molecule.

In another aspect, the present invention contemplates an apparatus for determining whether a compound is a potential inhibitor of a polypeptide having SEQ ID NO: 2 or SEQ

ID NO: 4, the apparatus comprising: (a) a memory that comprises: (i) the three dimensional coordinates and identities of the atoms of a polypeptide of the invention or a fragment thereof that form a druggable site; and (ii) executable instructions; and (b) a processor that is capable of executing instructions to: (i) receive three-dimensional structural information for a candidate compound; (ii) determine if the three-dimensional structure of the candidate compound is complementary to the structure of the interior of the druggable site; and (iii) output the results of the determination.

In another aspect, the present invention contemplates a method for designing a potential compound for the prevention or treatment of *E. faecalis* related disease or disorder, the method comprising: (a) providing the three dimensional structure of a crystallized polypeptide of the invention, or a fragment thereof; (b) synthesizing a potential compound for the prevention or treatment of *E. faecalis* related disease or disorder based on the three dimensional structure of the crystallized polypeptide or fragment; (c) contacting a polypeptide of the present invention or an *E. faecalis* with the potential compound; and (d) assaying the activity of a polypeptide of the present invention, wherein a change in the activity of the polypeptide indicates that the compound may be useful for prevention or treatment of a *E. faecalis* related disease or disorder.

In another aspect, the present invention contemplates a method for designing a potential compound for the prevention or treatment of *E. faecalis* related disease or disorder, the method comprising: (a) providing structural information of a druggable region derived from NMR spectroscopy of a polypeptide of the invention, or a fragment thereof; (b) synthesizing a potential compound for the prevention or treatment of *E. faecalis* related disease or disorder based on the structural information; (c) contacting a polypeptide of the present invention or an *E. faecalis* with the potential compound; and (d) assaying the activity of a polypeptide of the present invention, wherein a change in the activity of the polypeptide indicates that the compound may be useful for prevention or treatment of a *E. faecalis* related disease or disorder.

(b) In Vitro Assays

Polypeptides of the invention may be used to assess the activity of small molecules and other modulators in *in vitro* assays. In one embodiment of such an assay, agents are identified which modulate the biological activity of a protein, protein-protein interaction of interest or protein complex, such as an enzymatic activity, binding to other cellular

components, cellular compartmentalization, signal transduction, and the like. In certain embodiments, the test agent is a small organic molecule.

Assays may employ kinetic or thermodynamic methodology using a wide variety of techniques including, but not limited to, microcalorimetry, circular dichroism, capillary zone electrophoresis, nuclear magnetic resonance spectroscopy, fluorescence spectroscopy, and combinations thereof.

The invention also provides a method of screening compounds to identify those which modulate the action of polypeptides of the invention, or polynucleotides encoding the same. The method of screening may involve high-throughput techniques. For example, to screen for modulators, a synthetic reaction mix, a cellular compartment, such as a membrane, cell envelope or cell wall, or a preparation of any thereof, comprising a polypeptide of the invention and a labeled substrate or ligand of such polypeptide is incubated in the absence or the presence of a candidate molecule that may be a modulator of a polypeptide of the invention. The ability of the candidate molecule to modulate a polypeptide of the invention is reflected in decreased binding of the labeled ligand or decreased production of product from such substrate. Detection of the rate or level of production of product from substrate may be enhanced by using a reporter system. Reporter systems that may be useful in this regard include but are not limited to colorimetric labeled substrate converted into product, a reporter gene that is responsive to changes in a nucleic acid of the invention or polypeptide activity, and binding assays known in the art.

Another example of an assay for a modulator of a polypeptide of the invention is a competitive assay that combines a polypeptide of the invention and a potential modulator with molecules that bind to a polypeptide of the invention, recombinant molecules that bind to a polypeptide of the invention, natural substrates or ligands, or substrate or ligand mimetics, under appropriate conditions for a competitive inhibition assay. Polypeptides of the invention can be labeled, such as by radioactivity or a colorimetric compound, such that the number of molecules of a polypeptide of the invention bound to a binding molecule or converted to product can be determined accurately to assess the effectiveness of the potential modulator.

A number of methods for identifying a molecule which modulates the activity of a polypeptide are known in the art. For example, in one such method, a subject polypeptide is contacted with a test compound, and the activity of the subject polypeptide in the

presence of the test compound is determined, wherein a change in the activity of the subject polypeptide is indicative that the test compound modulates the activity of the subject polypeptide. In certain instances, the test compound agonizes the activity of the subject polypeptide, and in other instances, the test compound antagonizes the activity of the subject polypeptide.

In another example, a compound which modulates SEQ ID NO: 2 or SEQ ID NO: 4 dependent growth or infectivity of *E. faecalis* may be identified by (a) contacting a polypeptide of the invention with a test compound; and (b) determining the activity of the polypeptide in the presence of the test compound, wherein a change in the activity of the polypeptide is indicative that the test compound may modulate the growth or infectivity of *E. faecalis*.

(c) In Vivo Assays

Animal models of bacterial infection and/or disease may be used as an *in vivo* assay for evaluating the effectiveness of a potential drug target in treating or preventing diseases or disorders. A number of suitable animal models are described briefly below, however, these models are only examples and modifications, or completely different animal models, may be used in accord with the methods of the invention.

(i) Mouse Soft Tissue Model

The mouse soft tissue infection model is a sensitive and effective method for measurement of bacterial proliferation. In these models (Vogelman et al., 1988, J. Infect. Dis. 157: 287-298) anesthetized mice are infected with the bacteria in the muscle of the hind thigh. The mice can be either chemically immune compromised (e.g., cytoxan treated at 125 mg/kg on days -4, -2, and 0) or immunocompetent. The dose of microbe necessary to cause an infection is variable and depends on the individual microbe, but commonly is on the order of 10^5 - 10^6 colony forming units per injection for bacteria. A variety of mouse strains are useful in this model although Swiss Webster and DBA2 lines are most commonly used. Once infected the animals are conscious and show no overt ill effects of the infections for approximately 12 hours. After that time virulent strains cause swelling of the thigh muscle, and the animals can become bacteremic within approximately 24 hours. This model most effectively measures proliferation of the microbe, and this proliferation is measured by sacrifice of the infected animal and counting colonies from homogenized thighs.

(ii) Diffusion Chamber Model

A second model useful for assessing the virulence of microbes is the diffusion chamber model (Malouin et al., 1990, Infect. Immun. 58: 1247-1253; Doy et al., 1980, J. Infect. Dis. 2: 39-51; Kelly et al., 1989, Infect. Immun. 57: 344-350. In this model rodents have a diffusion chamber surgically placed in the peritoneal cavity. The chamber consists of a polypropylene cylinder with semipermeable membranes covering the chamber ends. Diffusion of peritoneal fluid into and out of the chamber provides nutrients for the microbes. The progression of the "infection" may be followed by examining growth, the exoproduct production or RNA messages. The time experiments are done by sampling multiple chambers.

(iii) Endocarditis Model

For bacteria, an important animal model effective in assessing pathogenicity and virulence is the endocarditis model (J. Santoro and M. E. Levinson, 1978, Infect. Immun. 19: 915-918). A rat endocarditis model can be used to assess colonization, virulence and proliferation.

(iv) Osteomyelitis Model

A fourth model useful in the evaluation of pathogenesis is the osteomyelitis model (Spagnolo et al., 1993, Infect. Immun. 61: 5225-5230). Rabbits are used for these experiments. Anesthetized animals have a small segment of the tibia removed and microorganisms are microinjected into the wound. The excised bone segment is replaced and the progression of the disease is monitored. Clinical signs, particularly inflammation and swelling are monitored. Termination of the experiment allows histolic and pathologic examination of the infection site to complement the assessment procedure.

(v) Murine Septic Arthritis Model

A fifth model relevant to the study of microbial pathogenesis is a murine septic arthritis model (Abdelnour et al., 1993, Infect. Immun. 61: 3879-3885). In this model mice are infected intravenously and pathogenic organisms are found to cause inflammation in distal limb joints. Monitoring of the inflammation and comparison of inflammation vs. inocula allows assessment of the virulence of related strains.

(vi) Bacterial Peritonitis Model

Finally, bacterial peritonitis offers rapid and predictive data on the virulence of strains (M. G. Bergeron, 1978, Scand. J. Infect. Dis. Suppl. 14: 189-206; S. D. Davis, 1975, Antimicrob. Agents Chemother. 8: 50-53). Peritonitis in rodents, such as mice, can provide essential data on the importance of targets. The end point may be lethality or clinical signs

can be monitored. Variation in infection dose in comparison to outcome allows evaluation of the virulence of individual strains.

A variety of other *in vivo* models are available and may be used when appropriate for specific pathogens or specific test agents. For example, target organ recovery assays (Gordee et al., 1984, J. Antibiotics 37:1054-1065; Bannatyne et al., 1992, Infect. 20:168-170) may be useful for fungi and for bacterial pathogens which are not acutely virulent to animals.

It is also relevant to note that the species of animal used for an infection model, and the specific genetic make-up of that animal, may contribute to the effective evaluation of the effects of a particular test agent. For example, immuno-incompetent animals may, in some instances, be preferable to immuno-competent animals. For example, the action of a competent immune system may, to some degree, mask the effects of the test agent as compared to a similar infection in an immuno-incompetent animal. In addition, many opportunistic infections, in fact, occur in immuno-compromised patients, so modeling an infection in a similar immunological environment is appropriate.

10. Vaccines

There are provided by the invention, products, compositions and methods for raising immunological response against a pathogen, especially *E. faecalis*. In one aspect, a polypeptide of the invention or a nucleic acid of the invention, or an antigenic fragment thereof, may be administered to a subject, optionally with a booster, adjuvant, or other composition that stimulates immune responses.

Another aspect of the invention relates to a method for inducing an immunological response in an individual, particularly a mammal which comprises inoculating the individual with a polypeptide of the invention and/or a nucleic acid of the invention, adequate to produce antibody and/or T cell immune response to protect said individual from infection, particularly bacterial infection and most particularly *E. faecalis* infection. Also provided are methods whereby such immunological response slows bacterial replication. Yet another aspect of the invention relates to a method of inducing immunological response in an individual which comprises delivering to such individual a nucleic acid vector, sequence or ribozyme to direct expression of a polypeptide of the invention and/or a nucleic acid of the invention *in vivo* in order to induce an immunological response, such as, to produce antibody and/or T cell immune response, including, for example, cytokine-

producing T cells or cytotoxic T cells, to protect said individual, preferably a human, from disease, whether that disease is already established within the individual or not. One example of administering the gene is by accelerating it into the desired cells as a coating on particles or otherwise. Such nucleic acid vector may comprise DNA, RNA, a ribozyme, a modified nucleic acid, a DNA/RNA hybrid, a DNA-protein complex or an RNA-protein complex.

A further aspect of the invention relates to an immunological composition that when introduced into an individual, preferably a human, capable of having induced within it an immunological response, induces an immunological response in such individual to a nucleic acid of the invention and/or a polypeptide encoded therefrom, wherein the composition comprises a recombinant nucleic acid of the invention and/or polypeptide encoded therefrom and/or comprises DNA and/or RNA which encodes and expresses an antigen of said nucleic acid of the invention, polypeptide encoded therefrom, or other polypeptide of the invention. The immunological response may be used therapeutically or prophylactically and may take the form of antibody immunity and/or cellular immunity, such as cellular immunity arising from CTL or CD4+T cells.

In another embodiment, the invention relates to compositions comprising a polypeptide of the invention and an adjuvant. The adjuvant can be any vehicle which would typically enhance the antigenicity of a polypeptide, e.g., minerals (for instance, alum, aluminum hydroxide or aluminum phosphate), saponins complexed to membrane protein antigens (immune stimulating complexes), pluronic polymers with mineral oil, killed mycobacteria in mineral oil, Freund's complete adjuvant, bacterial products, such as muramyl dipeptide (MDP) and lipopolysaccharide (LPS), as well as lipid A, liposomes, or any of the other adjuvants known in the art. A polypeptide of the invention can be emulsified with, absorbed onto, or coupled with the adjuvant.

A polypeptide of the invention may be fused with co-protein or chemical moiety which may or may not by itself produce antibodies, but which is capable of stabilizing the first protein and producing a fused or modified protein which will have antigenic and/or immunogenic properties, and preferably protective properties. Thus fused recombinant protein, may further comprise an antigenic co-protein, such as lipoprotein D from Hemophilus influenzae, Glutathione-S-transferase (GST) or beta-galactosidase, or any other relatively large co-protein which solubilizes the protein and facilitates production and purification thereof. Moreover, the co-protein may act as an adjuvant in the sense of

providing a generalized stimulation of the immune system of the organism receiving the protein. The co-protein may be attached to either the amino- or carboxy-terminus of a polypeptide of the invention.

Provided by this invention are compositions, particularly vaccine compositions, and methods comprising the polypeptides and/or polynucleotides of the invention and immunostimulatory DNA sequences, such as those described in Sato, Y. et al. Science 273: 352 (1996).

Also, provided by this invention are methods using the described polynucleotide or particular fragments thereof, which have been shown to encode non-variable regions of bacterial cell surface proteins, in polynucleotide constructs used in such genetic immunization experiments in animal models of infection with *E. faecalis*. Such experiments will be particularly useful for identifying protein epitopes able to provoke a prophylactic or therapeutic immune response. It is believed that this approach will allow for the subsequent preparation of monoclonal antibodies of particular value, derived from the requisite organ of the animal successfully resisting or clearing infection, for the development of prophylactic agents or therapeutic treatments of bacterial infection, particularly *E. faecalis* infection, in mammals, particularly humans.

A polypeptide of the invention may be used as an antigen for vaccination of a host to produce specific antibodies which protect against invasion of bacteria, for example by blocking adherence of bacteria to damaged tissue.

11. Array Analysis

In part, the present invention is directed to the use of subject nucleic acids in arrays to assess gene expression. In another part, the present invention is directed to the use of subject nucleic acids in arrays for *E. faecalis*. In yet another part, the present invention contemplates using the subject nucleic acids to interact with probes contained on arrays.

In one aspect, the present invention contemplates an array comprising a substrate having a plurality of addresses, wherein at least one of the addresses has disposed thereon a capture probe that can specifically bind to a nucleic acid of the invention. In another aspect, the present invention contemplates a method for detecting expression of a nucleotide sequence which encodes a polypeptide of the invention, or a fragment thereof, using the foregoing array by: (a) providing a sample comprising at least one mRNA molecule; (b) exposing the sample to the array under conditions which promote

hybridization between the capture probe disposed on the array and a nucleic acid complementary thereto; and (c) detecting hybridization between an mRNA molecule of the sample and the capture probe disposed on the array, thereby detecting expression of a sequence which encodes for a polypeptide of the invention, or a fragment thereof.

Arrays are often divided into microarrays and macroarrays, where microarrays have a much higher density of individual probe species per area. Microarrays may have as many as 1000 or more different probes in a 1 cm^2 area. There is no concrete cut-off to demarcate the difference between micro- and macroarrays, and both types of arrays are contemplated for use with the invention.

Microarrays are known in the art and generally consist of a surface to which probes that correspond in sequence to gene products (e.g., cDNAs, mRNAs, oligonucleotides) are bound at known positions. In one embodiment, the microarray is an array (e.g., a matrix) in which each position represents a discrete binding site for a product encoded by a gene (e.g., a protein or RNA), and in which binding sites are present for products of most or almost all of the genes in the organism's genome. In certain embodiments, the binding site or site is a nucleic acid or nucleic acid analogue to which a particular cognate cDNA can specifically hybridize. The nucleic acid or analogue of the binding site may be, e.g., a synthetic oligomer, a full-length cDNA, a less-than full length cDNA, or a gene fragment.

Although in certain embodiments the microarray contains binding sites for products of all or almost all genes in the target organism's genome, such comprehensiveness is not necessarily required. Usually the microarray will have binding sites corresponding to at least 100, 500, 1000, 4000 genes or more. In certain embodiments, arrays will have anywhere from about 50, 60, 70 , 80, 90, or even more than 95% of the genes of a particular organism represented. The microarray typically has binding sites for genes relevant to testing and confirming a biological network model of interest. Several exemplary human microarrays are publicly available.

The probes to be affixed to the arrays are typically polynucleotides. These DNAs can be obtained by, e.g., polymerase chain reaction (PCR) amplification of gene segments from genomic DNA, cDNA (e.g., by RT-PCR), or cloned sequences. PCR primers are chosen, based on the known sequence of the genes or cDNA, that result in amplification of unique fragments (e.g., fragments that do not share more than 10 bases of contiguous identical sequence with any other fragment on the microarray). Computer programs are useful in the design of primers with the required specificity and optimal amplification

properties. See, e.g., Oligo pl version 5.0 (National Biosciences). In an alternative embodiment, the binding (hybridization) sites are made from plasmid or phage clones of genes, cDNAs (e.g., expressed sequence tags), or inserts therefrom (Nguyen et al., 1995, Genomics 29:207-209).

A number of methods are known in the art for affixing the nucleic acids or analogues to a solid support that makes up the array (Schena et al., 1995, Science 270:467-470; DeRisi et al., 1996, Nature Genetics 14:457-460; Shalon et al., 1996, Genome Res. 6:639-645; and Schena et al., 1995, Proc. Natl. Acad. Sci. USA 93:10539-11286).

Another method for making microarrays is by making high-density oligonucleotide arrays (Fodor et al., 1991, Science 251:767-773; Pease et al., 1994, Proc. Natl. Acad. Sci. USA 91:5022-5026; Lockhart et al., 1996, Nature Biotech 14:1675; U.S. Pat. Nos. 5,578,832; 5,556,752; and 5,510,270; Blanchard et al., 1996, 11: 687-90).

Other methods for making microarrays, e.g., by masking (Maskos and Southern, 1992, Nuc. Acids Res. 20:1679-1684), may also be used. In principal, any type of array, for example, dot blots on a nylon hybridization membrane (see Sambrook et al., Molecular Cloning - A Laboratory Manual (2nd Ed.), Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1989), could be used, although, as will be recognized by those of skill in the art.

The nucleic acids to be contacted with the microarray may be prepared in a variety of ways, and may include nucleotides of the subject invention. Such nucleic acids are often labeled fluorescently. Nucleic acid hybridization and wash conditions are chosen so that the population of labeled nucleic acids will specifically hybridize to appropriate, complementary nucleic acids affixed to the matrix. Non-specific binding of the labeled nucleic acids to the array can be decreased by treating the array with a large quantity of non-specific DNA -- a so-called "blocking" step.

When fluorescently labeled probes are used, the fluorescence emissions at each site of a transcript array may be detected by scanning confocal laser microscopy. When two fluorophores are used, a separate scan, using the appropriate excitation line, is carried out for each of the two fluorophores used. Fluorescent microarray scanners are commercially available from Affymetrix, Packard BioChip Technologies, BioRobotics and many other suppliers. Signals are recorded, quantitated and analyzed using a variety of computer software.

According to the method of the invention, the relative abundance of an mRNA in two cells or cell lines is scored as a perturbation and its magnitude determined (i.e., the abundance is different in the two sources of mRNA tested), or as not perturbed (i.e., the relative abundance is the same). As used herein, a difference between the two sources of RNA of at least a factor of about 25% (RNA from one source is 25% more abundant in one source than the other source), more usually about 50%, even more often by a factor of about 2 (twice as abundant), 3 (three times as abundant) or 5 (five times as abundant) is scored as a perturbation. Present detection methods allow reliable detection of difference of an order of about 2-fold to about 5-fold, but more sensitive methods are expected to be developed.

In addition to identifying a perturbation as positive or negative, it is advantageous to determine the magnitude of the perturbation. This can be carried out, as noted above, by calculating the ratio of the emission of the two fluorophores used for differential labeling, or by analogous methods that will be readily apparent to those of skill in the art.

In certain embodiments, the data obtained from such experiments reflects the relative expression of each gene represented in the microarray. Expression levels in different samples and conditions may now be compared using a variety of statistical methods.

12. Pharmaceutical Compositions

Pharmaceutical compositions of this invention include any modulator identified according to the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The term "pharmaceutically acceptable carrier" refers to a carrier(s) that is "acceptable" in the sense of being compatible with the other ingredients of a composition and not deleterious to the recipient thereof.

Methods of making and using such pharmaceutical compositions are also included in the invention. The pharmaceutical compositions of the invention can be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally, or via an implanted reservoir. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra articular, intrasynovial, intrasternal, intrathecal, intralesional, and intracranial injection or infusion techniques.

Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 0.5 and about 75 mg/kg body weight per day of the modulators described herein are useful for the prevention and treatment of disease and conditions,

including *E. faecalis* mediated diseases and conditions. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations contain from about 20% to about 80% active compound.

13. Antimicrobial Agents

The polypeptides of the invention may be used to develop antimicrobial agents for use in a wide variety of applications. The uses are as varied as surface disinfectants, topical pharmaceuticals, personal hygiene applications (e.g., antimicrobial soap, deodorant or the like), additives to cell culture medium, and systemic pharmaceutical products. Antimicrobial agents of the invention may be incorporated into a wide variety of products and used to treat an already existing microbial infection/contamination or may be used prophylactically to suppress future infection/contamination.

The antimicrobial agents of the invention may be administered to a site, or potential site, of infection/contamination in either a liquid or solid form. Alternatively, the agent may be applied as a coating to a surface of an object where microbial growth is undesirable using nonspecific absorption or covalent attachment. For example, implants or devices (such as linens, cloth, plastics, heart pacemakers, surgical stents, catheters, gastric tubes, endotracheal tubes, prosthetic devices) can be coated with the antimicrobials to minimize adherence or persistence of bacteria during storage and use. The antimicrobials may also be incorporated into such devices to provide slow release of the agent locally for several weeks during healing. The antimicrobial agents may also be used in association with devices such as ventilators, water reservoirs, air-conditioning units, filters, paints, or other substances. Antimicrobials of the invention may also be given orally or systemically after transplantation, bone replacement, during dental procedures, or during implantation to prevent colonization with bacteria.

In another embodiment, antimicrobial agents of the invention may be used as a food preservative or in treating food products to eliminate potential pathogens. The latter use might be targeted to the fish and poultry industries that have serious problems with enteric pathogens which cause severe human disease. In a further embodiment, the agents of the invention may be used as antimicrobials for food crops, either as agents to reduce post harvest spoilage or to enhance host resistance. The antimicrobials may also be used as

preservatives in processed foods either alone or in combination with antibacterial food additives such as lysozymes.

In another embodiment, the antimicrobials of the invention may be used as an additive to culture medium to prevent or eliminate infection of cultured cells with a pathogen.

EXEMPLIFICATION

The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention in any way.

EXAMPLE 1 Isolation and Cloning of Nucleic Acid

Enterococcus faecalis is a facultative Gram-positive anaerobe bacteria that is associated with both community and hospital acquired infections. Approximately 80% of enteroccocal infections in humans are caused by *E. faecalis*. The most common enterococcal-associated nosocomial infections are infections of the urinary tract, followed by surgical wound infections and bacteremia. Other enterococcal infections include intra abdominal and pelvic infections, central nervous system infections, and in rare instances, osteomyelitis and pulmonary infections. The high virulence of the organism and the ability of many strains to resist numerous anti-microbial agents, presents difficult therapeutic issues. Most enterococci are relatively resistant to penicillin, ampicillin, and the ureidopenicillins. *E. faecalis* polynucleotide sequences were obtained from The Institute of Genomic Research (TIGR) (Rockville, MD; www.tigr.org). *E. faecalis* genomic DNA is extracted from a crushed cell pellet (strain *V583*) and and subjected to 10% sucrose and 2% SDS in a 60°C water bath, followed by the addition of 1 M NaCl for a 40 minute incubation on ice. Impurities, including RNA and proteins, are removed by enzymatic degradation via RNAse and phenol-chloroform extractions, respectively. The DNA is then precipitated, washed with ethanol, and quantified by UV absorption.

The coding sequences of the subject nucleic acid sequences (predicted) are obtained by reference to either publicly available databases or from the use of a bioinformatics program that is used to select the coding sequence of interest from the applicable genome. For example, bioinformatics programs that may be used to select the coding sequence of interest from the genome of *E. faecalis* include that described in Nucleic Acids Research,

1999, 27:4636-4641 and the ContigExpress and Translate functionalities of Vector NTI Suite (InforMax).

The coding DNA is amplified from purified genomic DNA using PCR with primers that are identified with a computer program. The PCR primers are selected so as to introduce restriction enzyme cleavage sites at the flanking regions of the DNA (e.g., NdeI and BglII). The forward and reverse primers have SEQ ID NO: 5 and SEQ ID NO: 6. The sequences of the primers are shown in FIGURE 5, and their respective restriction sites and melting temperatures are shown in Table 1 of FIGURE 6.

The PCR reaction is performed using 50-100 *ng* of chromosomal DNA and 2 Units of a high fidelity DNA Polymerase (for example *Pfu* Turbo (Stratagene) or Platinum *Pfx* (Invitrogen)). The thermocycling conditions for the PCR process include a DNA melting step at 94°C for 45 sec, a primer annealing step at 48°C - 58°C (depending on Primer [Tm]) for 45 sec, and an extension step at 68°C – 72°C (depending on enzyme) for 1 min 45 sec – 2 min 30 sec (depending on size of DNA). After 25-30 cycles, a final blocking step at 72°C for 9 min is carried out.

The amplified nucleic acid product is isolated from the PCR cocktail using silica-gel membrane based column chromatography (Qiagen). The quality of the PCR product is assessed by resolving an aliquot of amplified product on a 1% agarose gel. The DNA is quantified spectrophotometrically at A_{260} or by visualizing the resolved genes with a 302 nm UV-B light source.

The PCR product is directionally cloned into the polylinker region of any of three expression vectors: pET28 (Novagen), pET15 (Novagen) or pGEX (Pharmacia/LKB Biotechnology). Additional restriction enzyme sites may be engineered into the expressions vectors to allow for simultaneous clones to be prepared having different purification tags. After the ligation reaction, the DNA is transformed into competent *E. coli* cells (Strains XL1-Blue (Stratagene) or DH5α (Invitrogen)) via heat shock or electroporation as described in Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989). The expression vectors contain the bacteriophage T7 promoter for RNA polymerase, and the *E. coli* strain used produces T7 RNA polymerase upon induction with isopropyl-β-D-thiogalactoside (IPTG). The sequence of the cloning site adds a Glutathione S-transferase (GST) tag, or a polyhistidine (6X His) tag, at the N- or C– terminus of the recombinant protein. The cloning site also inserts a cleavage site for the thrombin or Tev (Invitrogen)

enzymes between the recombinant protein and the N- or C- terminal GST or polyhistidine tag.

Transformants are selected using the appropriate antibiotic (Ampicillin or Kanamycin) and identified using PCR, or another method, to analyze their DNA. The polynucleotide sequence cloned into the expression construct is then isolated using a modified alkaline lysis method (Birnboim, H.C., and Doly, J. (1979) *Nucl. Acids Res.* 7, 1513-1522.) The sequence of the clone is verified by standard polynucleotide sequencing methods. The published nucleic acid and amino acid sequences are presented in FIGURE 1 and FIGURE 2. The experimentally determined nucleic acid sequence is presented in FIGURE 3, and the amino acid sequence predicted from the sequence of FIGURE 3 is presented in FIGURE 4.

The expression construct is transformed into a bacterial host strain BL21-Gold (DE3) supplemented with a plasmid called pUBS520, which directs expression of tRNA for arginine (agg and aga) and serves to augment the expression of the recombinant protein in the host cell (Gene, vol. 85 (1989) 109-114). The expression construct may also be transformed into BL21-Gold (DE3) without pUBS520, BL21-Gold (DE3) Codon-Plus (RIL) or (RP) (Stratagene) or Roseatta (DE3) (Novagen), the latter two of which contain genes encoding tRNAs. Alternatively, the expression construct may be transformed into BL21 STAR *E. coli* (Invitrogen) cells which has an Rnase deficiency that reduces degradation of recombinant mRNA transcript and therefore increases the protein yield. The recombinant protein is then assayed for positive overexpression in the host and the presence of the protein in the cytoplasmic (water soluble) region of the cell.

EXAMPLE 2 Test Protein Expression and Solubility

(a) Test Expression

Transformed cells are grown in LB medium supplemented with the appropriate antibiotics up to a final concentration of 100 μg/ml. The cultures are shaken at 37°C until they reach an optical density (OD_{600}) between 0.6 and 0.7. The cultures are then induced with isopropyl-beta-D-thiogalactopyranoside (IPTG) to a final concentration of 0.5 mM at 15°C for 10 hours, 25°C for 4 hours, or 30°C for 4 hours.

(b) Method One for Determining Protein Solubility Levels

The cells are harvested by centrifugation and subjected to a freeze/thaw cycle. The cells are lysed using detergent, sonication, or incubation with lysozyme. Total and soluble

proteins are assayed using a 26-well BioRad Criterion gel running system. The proteins are stained with an appropriate dye (Coomassie, Silver stain, or Sypro-Red) and visualized with the appropriate visualization system. Typically, recombinant protein is seen as a prominent band in the lanes of the gel representing the soluble fraction.

(c) Method Two for Determining Protein Solubility Levels

The soluble and insoluble fractions (in the presence of 6M urea) of the cell pellet are bound to the appropriate affinity column. The purified proteins from both fractions are analysed by SDS-PAGE and the levels of protein in the soluble fraction are determined.

The approximate percent solubility of the polypeptide having the sequence of SEQ ID NO: 4 is determined using one of the foregoing methods, and the resulting percent solubility is presented in Table 1 of FIGURE 6.

EXAMPLE 3 Native Protein Expression

The expression construct clone encoding the soluble polypeptide having the amino acid sequence of SEQ ID NO: 4 is introduced into an expression host. The resultant cell line is then grown in culture. The method of growth is dependant on whether the protein to be purified is a native protein or a labeled protein. For native and ^{15}N labeled protein production, a Gold-pUBS520 (as described above), BL21-Gold (DE3) Codon-Plus (RIL) or (RP), or BL21 STAR *E. Coli* cell line is used. For generating proteins metabolically labeled with selenium, the clone is introduced into a strain called B834 (Novagen). The methods for expressing labeled polypeptides of the invention are described in the Examples that follow.

In one method for expressing an unlabeled polypeptide of the invention, 2L LB cultures or 1L TB cultures are inoculated with a 1% (v/v) starter culture (OD_{600} of 0.8). The cultures are shaken at 37°C and 200 rpm and grown to an OD_{600} of 0.6-0.8 followed by induction with 0.5mM IPTG at 15°C and 200 rpm for at least 10 hours or at 25°C for 4 hours.

The cells are harvested by centrifugation and the pellets are resuspended in 25 ml HEPES buffer (50 mM, pH 7.5), supplemented with 100µl of protease inhibitors (PMSF and benzamidine (Sigma)) and flash-frozen in liquid nitrogen.

Alternatively, for an unlabeled polypeptide of the invention, a starter culture is prepared in a 300 mL Tunair flask (Shelton Scientific) by adding 20 mL of medium having

47.6 g/L of Terrific Broth and 1.5% glycerol in dH_2O followed by autoclaving for 30 minutes at 121°C and 15 psi. When the broth cools to room temperature, the medium is supplemented with 6.3 µM $CoCl_2$-$6H_2O$, 33.2 µM $MnSO_4$-$5H_2O$, 5.9 µM $CuCl_2$-$2H_2O$, 8.1 µM H_3BO_3, 8.3 µM Na_2MoO_4-$2H_2O$, 7 µM $ZnSO_4$-$7H_2O$, 108 µM $FeSO_4$-$7H_2O$, 68 µM $CaCl_2$-$2H_2O$, 4.1 µM $AlCl_3$-$6H_2O$, 8.4 µM $NiCl_2$-$6H_2O$, 1 mM $MgSO_4$, 0.5% v/v of Kao and Michayluk vitamins mix (Sigma; Cat. No. K3129), 25 µg/mL Carbenicillin, and 50 µg/mL Kanamycin. The medium is then inoculated with several colonies of the freshly transformed expression construct of interest. The culture is incubated at 37°C and 260 rpm for about 3 hours and then transferred to a 2.5L Tunair Flask containing 1L of the above media. The 1L culture is then incubated at 37°C with shaking at 230-250 rpm on an orbital shaker having a 1 inch orbital diameter. When the culture reaches an OD_{600} of 3-6 it is induced with 0.5 mM IPTG. The induced culture is then incubated at 15°C with shaking at 230-250 rpm or faster for about 6-15 hours. The cells are harvested by centrifugation at 3500 rpm at 4°C for 20 minutes and the cell pellet is resuspended in 15 mL ice cold binding buffer (Hepes 50 mM, pH 7.5) and 100 µl of protease inhibitors (50 mM PMSF and 100 mM Benzamidine, stock concentration) and flash frozen.

EXAMPLE 4 Expression of Selmet Labeled Polypeptides

The freshly transformed cell, harboring a plasmid with a nucleic acid encoding a polypeptide of the invention, is inoculated into 20 ml of NMM (New Minimal Medium) and shaken at 37°C for 8-9 hours. This culture is then transferred into a 6L Erlenmeyer flask containing 2L of minimum medium (M9). The media is supplemented with all amino acids except methionine. All amino acids are added as a solution except for Tyrosine, Tryptophan and Phenylalanine which are added to the media in powder format. As well the media is supplemented with $MgSO_4$ (2mM final concentration), $FeSO_4.7H_2O$ (25mg/L final concentration), Glucose (0.4% final concentration), $CaCl_2$ (0.1mM final concentration) and Seleno-L-Methionine (40mg/L final concentration). When the OD_{600} of the cell culture reaches 0.8-0.9, IPTG (0.4 mM final concentration) is added to the medium for protein induction, and the cell culture is kept shaking at 15°C for 10 hours. The cells are harvested by centrifugation at 3500 rpm at 4°C for 20 minutes and the cell pellet is resuspended in 15 mL cold binding buffer (Hepes 50 mM, pH 7.5) and 100 µl of protease inhibitors (PMSF and Benzamidine) and flash frozen.

Alternatively, a starter culture is prepared in a 300 mL Tunair flask (Shelton Scientific) by adding 50 mL of sterile medium having 10% 10XM9 (37.4 mM NH_4Cl (Sigma; Cat. No. A4514), 44 mM KH_2PO_4 (Bioshop, Ontario, Canada; Cat. No. PPM 302), 96 mM Na_2HPO_4 (Sigma; Cat. No. S2429256), and 96 mM $Na_2HPO_4 \cdot 7H_2O$ (Sigma; Cat. No. S9390) final concentration), 450 μM alanine, 190 μM arginine, 302 μM asparagine, 300 μM aspartic acid, 330 μM cysteine, 272 μM glutamic acid, 274 μM glutamine, 533 μM glycine, 191 μM histidine, 305 μM isoleucine, 305 μM leucine, 220 μM lysine, 242 μM phenylalanine, 348 μM proline, 380 μM serine, 336 μM threonine, 196 μM tryptophan, 220 μM tyrosine, and 342 μM valine, 204 μM Seleno-L-Methionine (Sigma; Cat. No. S3132), 0.5% v/v of Kao and Michayluk vitamins mix (Sigma; Cat. No. K3129), 2 mM $MgSO_4$ (Sigma; Cat. No. M7774), 90 μM $FeSO_4 \cdot 7H_2O$ (Sigma; Cat. No. F8633), 0.4% glucose (Sigma; Cat. No. G-5400), 100 μM $CaCl_2$ (Bioshop, Ontario, Canada; Cat. No. CCL 302), 50 μg/mL Ampicillin, and 50 μg/mL Kanamycin in dH_2O. The medium is then inoculated with several colonies of *E. coli* B834 cells (Novagen) freshly transformed with an expression construct clone encoding the polypeptide of interest. The culture is then incubated at 37°C and 200 rpm until it reaches an OD_{600} of ~1 and is then transferred to a 2.5L Tunair Flask containing 1L of the above media. The 1L culture is incubated at 37°C with shaking at 200 rpm until the culture reaches an OD_{600} of 0.6-0.8 and is then induced with 0.5 mM IPTG. The induced culture is incubated overnight at 15°C with shaking at 200 rpm. The cells are harvested by centrifugation at 4200 rpm at 4°C for 20 minutes and the cell pellet is resuspended in 15 mL ice cold binding buffer (Hepes 50 mM, pH 7.5) and 100 μl of protease inhibitors (50 mM PMSF and 100 mM Benzamidine, stock concentration) and flash frozen.

Alternatively, the cell harboring a plasmid with a nucleic acid encoding a polypeptide of the invention is inoculated into 10 ml of M9 minimum medium and kept shaking at 37°C for 8-9 hours. This culture is then transferred into a 2L Baffled Flask (Corning) containing 1L minimum medium. The media is supplemented with all amino acids except methionine. All are added as a solution, except for Phenylalanine, Alanine, Valine, Leucine, Isoleucine, Proline, and Tryptophan which are added to the media in powder format. As well the media is supplemented with $MgSO_4$ (2mM final concentrtion), $FeSO_4 \cdot 7H_2O$ (25 mg/L final concentration), Glucose (0.5% final concentration), $CaCl_2$ (0.1 mM final concentration) and Seleno-Methionine (50 mg/L final concentration). When the

OD_{600} of the cell culture reaches 0.8-0.9, IPTG (0.8 mM final concentration) is added to the medium for protein induction, and the cell culture is kept shaking at 25°C for 4 hours. The cells are harvested by centrifuged at 3500 rpm at 4°C for 20 minutes and the cell pellet is resuspended in 10 mL cold binding buffer (Hepes 50 mM, pH 7.5) and 100 µl of protease inhibitors (PMSF and Benzamidine) and flash frozen.

EXAMPLE 5 Expression of ^{15}N Labeled Polypeptides

The cell, harboring a plasmid with a nucleic acid encoding a polypeptide of the invention, is inoculated into 2L of minimal media (containing ^{15}N isotope, Cambridge Isotope Lab) in a 6L Erlenmeyer flask. The minimal media is supplemented with 0.01 mM $ZnSO_4$, 0.1 mM $CaCl_2$, 1 mM $MgSO_4$, 5 mg/L Thiamine.HCl, and 0.4% glucose. The 2L culture is grown at 37°C and 200 rpm to an OD_{600} of between 0.7-0.8. The culture is then induced with 0.5 mM IPTG and allowed to shake at 15°C for 14 hours. The cells are harvested by centrifugation and the cell pellet is resuspended in 15 mL cold binding buffer and 100µl of protease inhibitor and flash frozen. The protein is then purified as described below.

Alternatively, the freshly transformed cell, harboring a plasmid with the gene of interest, is inoculated into 10 mL of M9 media (with ^{15}N isotope) and supplemented with with 0.01 mM $ZnSO_4$, 0.1 mM $CaCl_2$, 1 mM $MgSO_4$, 5 mg/L Thiamine.HCl, and 0.4% glucose. After 8-10 hours of growth at 37°C, the culture is transferred to a 2L Baffled flask (Corning) containing 990 mL of the same media. When OD_{600} of the culture is between 0.7-0.8, protein production is initiated by adding IPTG to a final concentration of 0.8 mM and lowering the temperature to 25°C. After 4 hours of incubation at this temperature, the cells are harvested, and the cell pellet is resuspended in 10 mL cold binding buffer (Hepes 50 mM, pH 7.5) and 100 µl of protease inhibitor and flash frozen.

EXAMPLE 6 Method One for Purifying Polypeptides of the Invention

The frozen pellets are thawed and sonicated to lyse the cells (5 x 30 seconds, output 4 to 5, 80% duty cycle, in a Branson Sonifier, VWR). The lysates are clarified by centrifugation at 14,000 rpm for 60 min at 4°C to remove insoluble cellular debris. The supernatants are removed and supplemented with 1 µl of Benzonase Nuclease (25 U/µl, Novagen).

The recombinant protein is purified using DE52 (anion exchanger, Whatman) and Ni-NTA columns (Qiagen). The DE52 columns (30 mm wide, Biorad) are prepared by mixing 10 grams of DE52 resin in 25 ml of 2.5 M NaCl per protein sample, applying the resin to the column and equilibrating with 30 ml of binding buffer (50 mM in HEPES, pH 7.5, 5% glycerol (v/v), 0.5 M NaCl, 5 mM imidazole). Ni-NTA columns are prepared by adding 3.5-8 ml of resin to the column (20 mm wide, Biorad) based on the level of expression of the recombinant protein and equilibrating the column with 30 ml of binding buffer. The columns are arranged in tandem so that the protein sample is first passed over the DE52 column and then loaded directly onto the Ni-NTA column.

The Ni-NTA columns are washed with at least 150 ml of wash buffer (50mM HEPES, pH 7.5, 5% glycerol (v/v), 0.5 M NaCl, 30 mM imidazole) per column. A pump may be used to load and/or wash the columns. The protein is eluted off of the Ni-NTA column using elution buffer (50 mM in HEPES, pH 7.5, 5% glycerol (v/v), 0.5 M NaCl, 250 mM imidazole) until no more protein is observed in the aliquots of eluate as measured using Bradford reagent (Biorad). The eluate is supplemented with 1 mM of EDTA and 0.2 mM DTT.

The samples are assayed by SDS-PAGE and stained with Coomassie Blue, with protein purity determined by visual staining.

Two methods may be used to remove the His tag located at either the C or N-terminus. In certain instances, the His tag may not be removed. In either case, the expressed polypeptide will have additional residues attributable to the His tag, as shown in the following table:

SEQ ID NO for Additional Residues	*Additional Residues*	*Type of Tag and Whether or Not Removed*
N/A	GSH	His tag removed from N-terminus
SEQ ID NO: 7	MGSSHHHHHHSSGLVPRGSH	His tag not removed from N-terminus
SEQ ID NO: 8	GSENLYFQGHHHHHH	His tag removed from C-terminus
SEQ ID NO: 9	GSENLYFQ	His tag not removed from C-terminus

In method one, a sample of purified polypeptide is supplemented with 2.5 mM $CaCl_2$ and an appropriate amount of thrombin (the amount added will vary depending on the activity of the enzyme preparation) and incubated for ~20-30 minutes on ice in order to

remove the His tag. In method two, a sample of purified polypeptide is combined with thirty units of recombinant TEV protease in 50 mmol TRIS HCl pH = 8.0, 0.5 mmol EDTA and 1 mmol DTT, followed by incubation at 4°C overnight, to remove the His tag.

The protein sample is then dialyzed in dialysis buffer (10mM HEPES, pH 7.5, 5% glycerol (v/v) and 0.5 M NaCl) for at least 8 hours using a Slide-A-Lyzer (Pierce) appropriate for the molecular weight of the recombinant protein. An aliquot of the cleaved and dialyzed samples is then assayed by SDS-PAGE and stained with Coomassie Blue to determine the purity of the protein and the success of cleavage.

The remainder of the sample is centrifuged at 2700 rpm at 4°C for 10-15 minutes to remove any precipitant and supplemented with 100 µl of protease inhibitor cocktail (0.1 M benzamidine and 0.05 M PMSF) (NO Bioshop). The protein is then applied to a second Ni-NTA column (~8 ml of resin) to remove the His-tags and eluted with binding buffer or wash buffer until no more protein is eluting off the column as assayed using the Bradford reagent. The eluted sample is supplemented with 1 mM EDTA and 0.6 mM of DTT and concentrated to a final volume of ~15 mls using a Millipore Concentrator with an appropriately sized filter at 2700 rpm at 4°C. The samples are then dialyzed overnight against crystallization buffer and concentrated to final volume of 0.3-0.7 ml.

EXAMPLE 7 Method Two for Purifying Polypeptides of the Invention

The frozen pellets are thawed and supplemented with 100 µl of protease inhibitor (0.1 M benzamidine and 0.05 M PMSF), 0.5% CHAPS, and 4 U/ml Benzonase Nuclease. The sample is then gently rocked on a Nutator (VWR, setting 3) at room temperature for 30 minutes. The cells are then lysed by sonication (1 x 30 seconds, output 4 to 5, 80% duty cycle, in a Branson Sonifier, VWR) and an aliquot is saved for a gel sample.

The recombinant protein is purified using a three column system. The columns are set up in tandem so that the lysate flows from a Biorad Econo (5.0 x 30 cm x 589 ml) "lysate" column onto a Biorad Econo (2.5 x 20 cm x 98 ml) DE52 column and finally onto a Biorad Econo (1.5 x 15 cm x 27 ml) Ni-NTA column. The lysate is mixed with 10 g of equilibrated DE52 resin and diluted to a total volume of 300 ml with binding buffer. This mixture is poured into the first column which is empty. The remainder of the purification procedure is described in EXAMPLE 6 above.

EXAMPLE 8 Method Three for Purifying Polypeptides of the Invention

The frozen pellets are thawed and sonicated to lyse the cells (5 x 30 seconds, output 4 to 5, 80% duty cycle, in a Branson Sonifier, VWR). The lysates are clarified by centrifugation at 14000 rpm for 60 min at 4°C to remove insoluble cellular debris. The supernatants are removed and supplemented with 1 µl of Benzonase Nuclease (25 U/µl, Novagen).

The recombinant protein is purified using DE52 (anion exchanger, Whatman) and Glutathione sepharose columns (Glutathione-Superflow resin, Clontech). The DE52 columns (30 mm wide, Biorad) are prepared by mixing 10 grams of DE52 resin in 20 ml of 2.5 M NaCl per protein sample, applying the resin to the column and equilibrating with 30 ml of loading buffer (50mM in HEPES, pH 7.5, 10% glycerol (v/v), 0.5 M NaCl, 1 mM EDTA, 1 mM DTT). Glutathione sepharose columns are prepared by adding 3 ml of resin to the column (20 mm wide, Biorad) and equilibrating the column with 30 ml of loading buffer. The columns are arranged in tandem so that the protein sample is first passed over the DE52 column and then loads directly onto the Glutathione sepharose column.

The columns are washed with at least 150 ml of loading buffer supplemented with protease inhibitor cocktail (0.1 M benzamidine and 0.05 M PMSF) per column. A pump may be used to load and/or wash the columns. The protein is eluted off of the Glutathione sepharose column using elution buffer (20mM HEPES, pH 7.5, 0.5 M NaCl, 1 mM EDTA, 1 mM DTT; 25 mM glutathione (reduced form)) until no more protein is observed in the aliquots of eluate as measured using Biorad Bradford reagent.

The GST tag may be removed using thrombin or other procedures known in the art. The protein samples are then dialyzed into crystallization buffer (10 mM Hepes, pH 7.5, 500 mM NaCl) to remove free glutathione and assayed by SDS-PAGE followed by staining with Coomassie blue. Prior to use or storage, the samples are concentrated to final volume of 0.3-0.5 ml.

Using one or more of the methods described above, purified polypeptide having SEQ ID NO: 4 is obtained in a yield of approximately 31.03 mg per liter of culture. The purified polypeptide is essentially the only protein visualized in the SDS-PAGE assay using Coomassie Blue described above, which is at least about 95% or greater purity. The polypeptide so expressed and purified is His tagged (having sequence GSENLYFQGHHHHHH) at the C-terminus as described above.

The protein samples so prepared and purified may be used in the biophysical studies that follow, with or without the His tag or the residual amino acids resulting from removal of the His tag. In certain instances, such as EXAMPLE 11, the polypeptide used may be a fusion protein with a specific tag.

A stable solution of purified polypeptide having SEQ ID NO: 4, prepared and purified as described above, may be prepared with 21.40 mg (or a lesser amount) of protein in one ml of either the dialysis or crystallization buffers (or possibly both) described above in EXAMPLE 7 or EXAMPLE 9, respectively.

\Certain of the foregoing information is also set forth in Table 1 of .FIGURE 6

For certain polypeptides of the invention, truncated polypeptides are prepared. Truncated polypeptides are generated via a "shot gun" approach whereby 1 to about 15 or more residues may be deleted from the N and/or C termini of the polypeptide of interest in a sequential pattern, in a variety of combinations of deletions. Alternatively, truncated polypeptides may be prepared by rational design, using multiple sequence alignments of the protein and other orthologues, secondary structure prediction and tertiary structure of a related protein (if available) as guiding tools. In such cases, from 1 to about 20 amino acids or more may be deleted from the N and/or C termini. Truncated constructs are PCR amplified from genomic DNA and cloned into expression vectors as described above for the various pathogens. Truncation constructs are then tested for expression and solubility as described above. The most highly expressed and soluble truncated polypeptides may be subject to further purification and characterization as provided herein.

EXAMPLE 9 Mass Spectrometry Analysis via Fingerprint Mapping

A gel slice from a purification protocol described above containing a polypeptide of the invention is cut into 1 mm cubes and 10 to 20 µl of 1% acetic acid is added. After washing with 100 - 150 µl HPLC grade water and removal of the liquid, acetonitrile (~200 µl, approximately 3 to 4 times the volume of the gel particles) is added followed by incubation at room temperature for 10 to 15 minutes with vortexing. A second acetonitrile wash may be required to completely dehydrate the gel particles. The protein in the gel particles is reduced at 50 degrees Celsius using 10 mM dithiothreitol (in 100 mM ammonium bicarbonate) and then alkylated at room temperature in the dark using 55 mM iodoacetamide (in 100 mM ammonium bicarbonate). The gel particles are rinsed with a

minimal volume of 100 mM ammonium bicarbonate before a trypsin (50 mM ammonium bicarbonate, 5 mM $CaCl_2$, and 12.5 ng/μl trypsin) solution is added. The gel particles are left on ice for 30 to 45 minutes (after 20 minutes incubation more trypsin solution is added). The excess trypsin solution is removed and 10 to 15 μl digestion buffer without trypsin is added to ensure the gel particles remain hydrated during digestion. After digestion at 37°C, the supernatant is removed from the gel particles. The peptides are extracted from the gel particles with 2 changes of 100 μL of 100 mM ammonium bicarbonate with shaking for 45 minutes and pooled with the initial gel supernatant. The extracts are acidified to 1% (v/v) with 100% acetic acid.

The tryptic peptides are purified with a C18 reverse phase resin. 250 μL of dry resin is washed twice with methanol and twice with 75% acetonitrile/1% acetic acid. A 5:1 slurry of solvent:resin is prepared with 75% acetonitrile/1% acetic acid. To the extracted peptides, 2 μL of the resin slurry is added and the solution is shaken for 30 minutes at room temperature. The supernatant is removed and replaced with 200 μL of 2% acetonitrile/1% acetic acid and shaken for 5-15 minutes. The supernatant is removed and the peptides are eluted from the resin with 15 μL of 75% acetonitrile/1% acetic acid with shaking for about 5 minutes. The peptide and slurry mixture is applied to a filter plate and centrifuged, and the filtrate is collected and stored at –70°C until use.

Alternatively, the tryptic peptides are purified using $ZipTip_{C18}$ (Millipore, Cat # ZTC18S960). The ZipTips are first pre-wetted by aspirating and dispensing 100% methanol. The tips are then washed with 2% acetonitrile/1% acetic acid (5 times), followed by 65% acetonitrile/1% acetic (5 times) and returned to 2% acetonitrile/1% acetic acid (10 times). The digested peptides are bound to the ZipTips by aspirating and dispensing the samples 5 times. Salts are removed by washing ZipTips with 2% acetonitrile/1% acetic acid (5 times). 10 μL of 65% acetonitrile/1% acetic acid is collected by the ZipTips and dispensed into a 96-well microtitre plate.

Analytical samples containing tryptic peptides are subjected to MALDI-TOF mass spectrometry. Samples are mixed 1:1 with a matrix of α-cyano-4-hydroxy-*trans*-cinnamic acid. The sample/matrix mixture is spotted on to the MALDI sample plate with a robot, either a Gilson 215 liquid handler or BioMek FX laboratory automation workstation (Beckman). The sample/matrix mixture is allowed to dry on the plate and is then introduced into the mass spectrometer. Analysis of the peptides in the mass spectrometer is

conducted using both delayed extraction mode (400 ns delay) and an ion reflector to ensure high resolution of the peptides.

Internally-calibrated tryptic peptide masses are searched against databases using a correlative mass matching algorithm. The Proteometrics software package (ProteoMetrics) is utilized for batch database searching of tryptic peptide mass spectra. Statistical analysis is performed on each protein match to determine its validity. Typical search constraints include error tolerances within 0.1 Da for monoisotopic peptide masses, carboxyamidomethylation of cysteines, no oxidation of methionines allowed, and 0 or 1 missed enzyme cleavages. The software calculates the probability that a candidate in the database search is the protein being analyzed, which is expressed as the Z-score. The Z-score is the distance to the population mean in unit of standard deviation and corresponds to the percentile of the search in the random match population. If a search is in the 95th percentile, for example, about 5% of random matches could yield a higher Z-score than the search. A Z-score of 1.282 for a search indicates that the search is in the 90th percentile, a Z-score of 1.645 indicates that the search is in the 95th percentile, a Z-score of 2.326 indicates that the search is in the 99th percentile, and a Z-score of 3.090 indicates that the search is in the 99.9th percentile.

As shown in FIGURE 8, and listed in Table 1 of FIGURE 6, are the results of the mass search described above. The Z-score for the polypeptide of the present invention is 2.41. The number of matched peptides for the polypeptide of the present invention is 14. The minimum sequence coverage for the polypeptide of the present invention is 31%. From this experiment, the identity of the subject polypeptide has been confirmed.

EXAMPLE 10 Mass Spectrometry Analysis via High Mass

A matrix solution of 25 mg/mL of 3,5-dimethoxy-4-hydroxycinnamic acid (sinapinic acid) in 66% (v/v) acetonitrile/1% (v/v) acetic acid is prepared along with an internal calibrant of carbonic anhydrase. On to a stainless steel polished MALDI target, 1.5 μL of a protein solution (concentration of 2 μg/μL) is spotted, followed immediately by 1.5 μL of matrix. 3 μL of 40% (v/v) acetonitrile/1% (v/v) acetic acid is then added to each spot has dried. The sample is either spotted manually or utilizing a Gilson 215 liquid handler or BioMek FX laboratory automation workstation (Beckman). The MALDI-TOF instrument utilizes positive ion and linear detection modes. Spectra are acquired automatically over a

mass to charge range from 0-150,000 Da, pulsed ion extraction delay is set at 200 ns, and 600 summed shots of 50-shot steps are completed.

The theoretical molecular weight of the protein for MALDI-TOF is determined from its amino acid sequence, taking into account any purification tag or residue thereof still present and any labels (e.g., selenomethionine or ^{15}N). To account for ^{15}N incorporation, an amount equal to the theoretical molecular weight of the protein divided by 70 is added. The mass of water is subtracted from the overall molecular weight. The MALDI-TOF spectrum is calibrated with the internal calibrant of carbonic anhydrase (observed as either $[MH^{+}_{avg}]$ 29025 or $[MH_2^{2+}]$ 14513).

FIGURE 9 displays a MALDI-TOF-generated mass spectrum of the intact polypeptide of the present invention. The experimentally determined molecular weight of the polypeptide is listed in Table 1 of FIGURE 6. In certain instances, a lower mass to charge peak may also be present, which signifies the presence of doubly-charged molecular ion peak $[MH_2^{2+}]$ of the protein.

EXAMPLE 11 Method One for Isolating and Identifying Interacting Proteins

(a) Method One for Preparation of Affinity Column

Micro-columns are prepared using forceps to bend the ends of P200 pipette tips and adding 10 µl of glass beads to act as a column frit. Six micro-columns are required for every polypeptide to be studied. The micro-columns are placed in a 96-well plate that has 1 mL wells. Next, a series of solutions of the polypetide having SEQ ID NO: 4 or other polypeptide of the invention, prepared and purified as described above and with a GST tag on either terminus, is prepared so as to give final amounts of 0, 0.1, 0.5, 1.0, and 2.0 mg of ligand per ml of resin volume.

A slurry of Glutathione-Sepharose 4B (Amersham) is prepared and 0.5 ml slurry/ligand is removed (enough for six 40-µg aliquots of resin). Using a glass frit Buchner funnel, the resin is washed sequentially with three 10 ml portions each of distilled H_2O and 1 M ACB (20 mM HEPES pH 7.9, 1 M NaCl, 10% glycerol, 1 mM DTT, and 1 mM EDTA). The Glutathione-Sepharose 4B is completely drained of buffer, but not dried. The Glutathione-Sepharose 4B is resuspended as a 50% slurry in 1 M ACB and 80 µl is added to each micro-column to obtain 40 µg/column. The buffer containing the ligand concentration series is added to the columns and allowed to flow by gravity. The resin and

ligand are allowed to cross-link overnight at 4°C. In the morning, micro-columns are washed with 100 µl of 1 M ACB and allowed to flow by gravity. This is repeated twice more and the elutions are tested for cross-linking efficiency by measuring the amount of unbound ligand. After washing, the micro-columns are equilibrated using 200 µl of 0.1 M ACB (20 mM HEPES pH 7.5, 0.1 M NaCl, 10% glycerol, 1 mM DTT, 1 mM EDTA).

In another method, the recombinant GST fusion protein can be replaced by a hexa-histidine fusion peptide for use with NTA-Agarose (Qiagen) as the solid support. No adaptation to the above protocol is required for the substitution of NTA agarose for GST Sepharose except that the recombinant protein requires a six histidine fusion peptide in place of the GST fusion.

(b) Method Two for Preparation of Affinity Column

In an alternative method, GST-Sepharose 4B may be replaced by Affi-gel 10 Gel (Bio-Rad). The column resin for affinity chromatography could also be Affigel 10 resin which allows for covalent attachment of the protein ligand to the micro affinity column. An adaptation to the above protocol for the use of this resin is a pre-wash of the resin with 100% isopropanol. No fusion peptides or proteins are required for the use of Affigel 10 resin.

(c) Method One for Bacterial Extract Preparation

An *E. faecalis* extract is prepared from cell pellets using a French press followed by sonication. An *E. faecalis* cell pellet (~6 g) is suspended in 3 pellet volumes (~20 ml final volume) of 20 mM HEPES pH 7.5, 150 mM NaCl, 10% glycerol, 10 mM $MgSO_4$, 10 mM $CaCl_2$, 1 mM DTT, 1 mM PMSF, 1 mM benzamidine, 40 µg/ml RNAse A, 75 units/ml S1 nuclease, and 40 units/ml DNAse 1. The cell suspension is lysed with one pass with a French Pressure Cell followed by sonication on ice using three bursts of 20 seconds each. The lysate is agitated at 4°C for 30 minutes, brought up to 0.5 M NaCl and then incubated for an additional 30 min at 4°C with agitation. The lysate is centrifuged at 20,000 rpm for 1 hr in a JA25.50 Beckman rotor. The supernatant is removed and dialyzed overnight in a 3,500 Mr dialysis membrane against dialysis buffer (20 mM HEPES pH 7.5, 10 % glycerol, 1 mM DTT, 1 mM EDTA, 100 mM NaCl, 10 mM $MgSO_4$, 10 mM $CaCl_2$, 1 mM benzamidine, and 1 mM PMSF). The dialyzed protein extract is removed from the dialysis tubing and frozen in one ml aliquots at –70°C.

(d) Method Two for Bacterial Extract Preparation

Bacterial cell extracts from *E. faecalis* are prepared from cell pellets using a Bead-Beater apparatus (Bio-spec Products Inc.) and zirconia beads (0.1 mm diameter). The bacterial cell pellet is suspended (~6 g) is suspended in 3 pellet volumes (~20 ml final volume) of 20 mM HEPES pH 7.5, 150 mM NaCl, 10% glycerol, 10 mM $MgSO_4$, 10 mM $CaCl_2$, 1 mM DTT, 1 mM PMSF, 1 mM benzamidine, 40 µg/ml RNAse A, 75 units/ml S1 nuclease, and 40 units/ml DNAse 1. The cells are lysed with 10 pulses of 30 sec between 90 sec pauses at a temperature of -5 °C. The lysate is separated from the zirconia beads using a standard column apparatus. The lysate is centrifuged at 20000 rpm (48000 x g) in a Beckman JA25.50 rotor. The supernatant is removed and dialyzed overnight at 4 °C against dialysis buffer (20 mM HEPES pH 7.5, 10 % glycerol, 1 mM DTT, 1 mM EDTA, 100 mM NaCl, 10 mM $MgSO_4$, 10 mM $CaCl_2$, 1 mM benzamidine, and 1 mM PMSF). The dialyzed protein extract is removed from the dialysis tubing and frozen in one ml aliquots at –70°C.

(e) HeLa Cell Extract Preparation

A HeLa cell extract is prepared in the presence of protease inhibitors. Approximately 30 g of Hela cells are submitted to a freeze/thaw cycle and then divided into two tubes. To each tube 20 ml of Buffer A (10 mM HEPES pH 7.9, 1.5 mM MgCl, 10 mM KCl, 0.5 mM DTT, 0.5 mM PMSF) and a protease inhibitor cocktail are added. The cell suspension is homogenized with 10 strokes (2 x 5 strokes) to lyse the cells. Buffer B (15 ml per tube) is added (50 mM HEPES pH 7.9, 1.5 mM MgCl, 1.26 M NaCl, 0.5 mM DTT, 0.5 mM PMSF, 0.5 mM EDTA, 75% glycerol) to each tube followed by a second round of homogenization (2 x 5 strokes). The lysates are stirred on ice for 30 minutes followed by centrifugation 37,000 rpm for 3 hr at 4°C in a Ti70 fixed angle Beckman rotor. The supernatant is removed and dialyzed overnight in a 10,000 Mr dialysis membrane against dialysis buffer (20 mM HEPES pH 7.9, 10% glycerol, 1 mM DTT, 1 mM EDTA, and 1 M NaCl. The dialyzed protein extract is removed from the dialysis tubing and frozen in one ml aliquots at –70°C.

(f) Affinity Chromatography

Cell extract is thawed and diluted to 5 mg/ml prior to loading 5 column volumes onto each micro-column. Each column is washed with 5 column volumes of 0.1 M ACB. This washing is repeated once. Each column is then washed with 5 column volumes of 0.1 M ACB containing 0.1% Triton X-100. The columns are eluted with 4 column volumes of 1% sodium dodecyl sulfate into a 96 well PCR plate. To each eluted fraction is added one-tenth volume of 10-fold concentrated loading buffer for SDS-PAGE.

(g) Resolution of the Eluted Proteins and Detection of Bound Proteins

The components of the eluted samples are resolved on SDS-polyacrylamide gels containing 13.8% polyacrylamide using the Laemmli buffer system and stained with silver nitrate. The bands containing the interacting protein are excised with a clean scalpel. The gel volume is kept to a minimum by cutting as close to the band as possible. The gel slice is placed into one well of a low protein binding, 96-well round-bottom plate. To the gel slices is added 20 µl of 1% acetic acid.

EXAMPLE 12 Method Two for Isolating and Identifying Interacting Proteins

Interacting proteins may be isolated using immunoprecipitation. Naturally-occurring bacterial or eukaryotic cells are grown in defined growth conditions or the cells can be genetically manipulated with a protein expression vector. The protein expression vector is used to transiently transfect the cDNA of interest into eukaryotic or prokaryotic cells and the protein is expressed for up to 24 or 48 hours. The cells are harvested and washed three times in sterile 20 mM HEPES (pH7.4)/Hanks balanced salts solution (H/H). The cells are finally resuspended in culture media and incubated at 37°C for 4-8 hr.

The harvested cells may be subjected to one or more culture conditions that may alter the protein profile of the cells for a given period of time. The cells are collected and washed with ice-cold H/H that includes 10 mM sodium pyrophosphate, 10 mM sodium fluoride, 10 mM EDTA, and 1 mM sodium orthovanadate. The cells are then lysed in lysis buffer (50 mM Tris-HCl (pH 8.0), 150 mM NaCl, 1% Triton X-100, 10 mM sodium pyrophosphate, 10mM sodium fluoride, 10 mM EDTA, 1 mM sodium orthovanadate, 1 µg/mL PMSF, 1 µg/mL aprotinin, 1 µg/mL leupeptin, and 1 µg/mL pepstatin A) by gentle mixing, and placed on ice for 5 minutes. After lysis, the lysate is transferred to centrifuge tubes and centrifuged in an ultracentrifuge at 75000 rpm for 15 min at 4°C. The supernatant is transferred to eppendorf tubes and pre-cleared with 10 µl of rabbit pre-immune antibody on a rotator at 4°C for 1 hr. Forty µl of protein A-Sepharose (Amersham) is then added and incubated at 4°C overnight on a rotator.

The protein A-Sepharose beads are harvested and the supernatant removed to a fresh eppendorf tube. Immune antibody is added to supernatant and rotated for 1 hr at 4°C. Thirty µl of protein A-Sepharose is then added and the mixture is further rotated at 4°C for 1 hr. The beads are harvested and the supernatant is aspirated. The beads are washed three

times with 50 mM Tris (pH 8.0), 150 mM NaCl, 0.1% Triton X-100, 10 mM sodium fluoride, 10 mM sodium pyrophosphate, 10 mM sodium orthovanadate, and 10 mM EDTA. Dry the beads with a 50 µl Hamilton syringe. Laemmli loading buffer containing 100 mM DTT is added to the beads and samples are boiled for 5 min. The beads are spun down and the supernatant is loaded onto SDS-PAGE gels. Comparison of the control and experimental samples allows for the selection of polypeptides that interact with the protein of interest.

EXAMPLE 13 Sample for Mass Spectrometry of Interacting Proteins

The gel slices are cut into 1 mm cubes and 10 to 20 µl of 1% acetic acid is added. The gel particles are washed with 100 - 150 µl of HPLC grade water (5 minutes with occasional mixing), briefly centrifuged, and the liquid is removed. Acetonitrile (~200 µl, approximately 3 to 4 times the volume of the gel particles) is added followed by incubation at room temperature for 10 to 15 minutes with vortexing. A second acetonitrile wash may be required to completely dehydrate the gel particles. The sample is briefly centrifuged and all the liquid is removed.

The protein in the gel particles is reduced at 50 degrees Celsius using 10 mM dithiothreitol (in 100 mM ammonium bicarbonate) for 30 minutes and then alkylated at room temperature in the dark using 55 mM iodoacetamide (in 100 mM ammonium bicarbonate). The gel particles are rinsed with a minimal volume of 100 mM ammonium bicarbonate before a trypsin (50 mM ammonium bicarbonate, 5 mM $CaCl_2$, and 12.5 ng/µl trypsin) solution is added. The gel particles are left on ice for 30 to 45 minutes (after 20 minutes incubation more trypsin solution is added). The excess trypsin solution is removed and 10 to 15 µl digestion buffer without trypsin is added to ensure the gel particles remain hydrated during digestion. The samples are digested overnight at 37°C.

The following day, the supernatant is removed from the gel particles. The peptides are extracted from the gel particles with 2 changes of 100 µL of 100 mM ammonium bicarbonate with shaking for 45 minutes and pooled with the initial gel supernatant. The extracts are acidified to 1% (v/v) with 100% acetic acid.

(a) Method One for Purification of Tryptic Peptides

The tryptic peptides are purified with a C18 reverse phase resin. 250 µL of dry resin is washed twice with methanol and twice with 75% acetonitrile/1% acetic acid. A 5:1

slurry of solvent : resin is prepared with 75% acetonitrile/1% acetic acid. To the extracted peptides, 2 μL of the resin slurry is added and the solution is shaken at moderate speed for 30 minutes at room temperature. The supernatant is removed and replaced with 200 μL of 2% acetonitrile/1% acetic acid and shaken for 5-15 minutes with moderate speed. The supernatant is removed and the peptides are eluted from the resin with 15 μL of 75% acetonitrile/1% acetic acid with shaking for about 5 minutes. The peptide and slurry mixture is applied to a filter plate and centrifuged for 1-2 minutes at 1000 rpm, the filtrate is collected and stored at –70°C until use.

(b) Method Two for Purification of Tryptic Peptides

Alternatively, the tryptic peptides may be purified using $ZipTip_{C18}$ (Millipore, Cat # ZTC18S960). The ZipTips are first pre-wetted by aspirating and dispensing 100% methanol 5 times. The tips are then washed with 2% acetonitrile/1% acetic acid (5 times), followed by 65% acetonitrile/1% acetic (5 times) and returned to 2% acetonitrile/1% acetic acid (5 times). The ZipTips are replaced in their rack and the residual solvent is eliminated. The ZipTips are washed again with 2% acetonitrile/1% acetic acid (5 times). The digested peptides are bound to the ZipTips by aspirating and dispensing the samples 5 times. Salts are removed by washing ZipTips with 2% acetonitrile/1% acetic acid (5 times). 10 μL of 65% acetonitrile/1% acetic acid is collected by the ZipTips and dispensed into a 96-well microtitire plate. 1 μL of sample and 1 μL of matrix are spotted on a MALDI-TOF sample plate for analysis.

EXAMPLE 14 Mass Spectrometric Analysis of Interacting Proteins

(a) Method One for Analysis of Tryptic Peptides

Analytical samples containing tryptic peptides are subjected to Matrix Assisted Laser Desorption/Ionization Time Of Flight (MALDI-TOF) mass spectrometry. Samples are mixed 1:1 with a matrix of α-cyano-4-hydroxy-*trans*-cinnamic acid. The sample/matrix mixture is spotted on to the MALDI sample plate with a robot. The sample/matrix mixture is allowed to dry on the plate and is then introduced into the mass spectrometer. Analysis of the peptides in the mass spectrometer is conducted using both delayed extraction mode and an ion reflector to ensure high resolution of the peptides.

Internally-calibrated tryptic peptide masses are searched against both in-house proprietary and public databases using a correlative mass matching algorithm. Statistical

analysis is performed on each protein match to determine its validity. Typical search constraints include error tolerances within 0.1 Da for monoisotopic peptide masses and carboxyamidomethylation of cysteines. Identified proteins are stored automatically in a relational database with software links to SDS-PAGE images and ligand sequences.

(b) Method Two for Analysis of Tryptic Peptides

Alternatively, samples containing tryptic peptides are analyzed with an ion trap instrument. The peptide extracts are first dried down to approximately 1 μL of liquid. To this, 0.1% trifluoroacetic acid (TFA) is added to make a total volume of approximately 5 μL. Approximately 1-2 μL of sample are injected onto a capillary column (C8, 150 μm ID, 15 cm long) and run at a flow rate of 800 nL/min. using the following gradient program:

Time (minutes)	% Solvent A	% Solvent B
0	95	5
30	65	35
40	20	80
41	95	5

Where Solvent A is composed of water/0.5% acetic acid and Solvent B is acetonitrile/0.5% acetic acid. The majority of the peptides will elute between the 20-40 % acetonitrile gradient. Two types of data from the eluting HPLC peaks are acquired with the ion trap mass spectrometer. In the MS^1 dimension, the mass to charge range for scanning is set at 400-1400 - this will determine the parent ion spectrum. Secondly, the instrument has MS^2 capabilities whereby it will acquire fragmentation spectra of any parent ions whose intensities are detected to be greater than a predetermined threshold (Mann and Wilm, *Anal Chem* 66(24): 4390-4399 (1994)). A significant amount of information is collected for each protein sample as both a parent ion spectrum and many daughter ion spectra are generated with this instrumentation.

All resulting mass spectra are submitted to a database search algorithm for protein identification. A correlative mass algorithm is utilized along with a statistical verification of each match to identify a protein's identification (Ducret A, et al., *Protein Sci* 7(3): 706-719 (1998)). This method proves much more robust than MALDI-TOF mass spectrometry for identifying the components of complex mixtures of proteins.

The identity of those interactor(s) are: ribosomal protein L23 (TIGR)-EF0208, ribosomal protein S3 (TIGR)-EF0212, ribosomal protein S5 (TIGR)-EF0224, ribosomal

protein L19 (TIGR)-EF1898, ribosomal protein S4 (TIGR)-EF3070 , ribosomal protein S2 (TIGR)-EF2398 , 22 and 30 kDa unidentified proteins.

EXAMPLE 15 NMR Analysis

Purified protein sample is centrifuged at 13,000 rpm for 10 minutes with a bench-top microcentrifuge to eliminate any precipitated protein. The supernatant is then transferred into a clean tube and the sample volume is measured. If the sample volume is less than 450 µl, an appropriate amount of crystal buffer is added to the sample to reach that volume. Then 50 µl of D_2O (99.9%) is added to the sample to make an NMR sample of 500 µl. The usual concentration of the protein sample is usually approximately 1 mmol or greater.

NMR screening experiments are performed on a Bruker AV600 spectrometer equipped with a cryoprobe, or other equivalent instrumentation. All spectra are recorded at 25°C. Standard 1D proton pulse sequence with presaturation is used for 1D screening. Normally, a sweepwidth of 6400 Hz, and eight or sixteen scans are used, although different pulse sequences are known to those of skill in the art and may be readily determined. For ^{1}H, ^{15}N HSQC experiments, a pulse sequence with "flip-back" water suppression may be used. Typically, sweepwidths of 8000 Hz and 2000 Hz are used for F2 and F1 dimension, respectively. Four to sixteen scans are normally adequate. The data is then processed on a Sun Ultra 5 computer with NMRpipe software.

EXAMPLE 16 X-ray Crystallography

(a) Crystallization

Suitable crystals for x-ray experimentation were obtained by vapor diffusion against a 100 ml reservoir solution containing 11% PEG4000 as a precipitant, 2% ethylene glycol, 9% isopropanol, and 100mM HEPES pH 7.4 in a 96 well sitting plate format, setting 1.5µl 15 mg/ml protein and 1.5 µl reservoir solutions in each drop. The crystals were soaked for 1 minute in a solution consisting of three parts mother liquor (from the well of the drop) to one part glycerol, and were then frozen at 100K in a cold gas stream. The crystal diffracted to a minimum d-spacing of 2.3 Å.

(b) Co-Crystallization

A variety of methods known in the art may be used for preparation of co-crystals comprising a polypeptide of the invention and one or more compounds that interact with the subject polypeptides, such as, for example, an inhibitor, co-factor, substrate, polynucleotide, polypeptide, and/or other molecule. In one exemplary method, crystals of the subject polypeptide may be soaked, for an appropriate period of time, in a solution containing a compound that interacts with a subject polypeptide. In another method, solutions of the subject polypeptide and/or compound that interacts with the subject polypeptide may be prepared for crystallization as described above and mixed into the above-described sitting drops. In certain embodiments, the molecule to be co-crystallized with the subject polypeptide may be present in the buffer in the sitting drop prior to addition of the solution comprising the subject polypeptide. In other embodiments, the subject polypeptide may be mixed with another molecule before adding the mixture to the sitting drop. Based on the teachings herein, one of skill in the art may determine the co-crystallization method yielding a co-crystal comprising the subject polypeptide.

(c) Heavy Atom Substitution

For preparation of crystals containing heavy atoms, crystals of the subject polypeptide may be soaked in a solution of a compound containing the appropriate heavy atom for such period as time as may be experimentally determined is necessary to obtain a useful heavy atom derivative for x-ray purposes. Likewise, for other compounds that may be of interest, including, for example, inhibitors or other molecules that interact with the subject polypeptide, crystals of the subject polypeptide may be soaked in a solution of such compound for an appropriate period of time.

(d) Data collection and processing

Data was collected from these crystals at APS, Illinois, COMCAT beamline. All data were processed using the HKL2000 software package. Crystals proved to be of the orthorhombic space group $P2_12_12_1$ with cell dimensions a = 76.434 Å, b = 112.876 Å, c = 125.792 Å, $\alpha = \beta = \gamma = 90°$.

The *E. faecalis HisS* protein structure was solved by molecular replacement using the coordinates of the Staphylococcus aureus *HisS* dimer (PDB ID 1QE0; amino acid identity 47%) as the search model for molecular replacement using EPMR. Ten percent of the reflections were randomly excluded from the refinement, and used to monitor Rfree in CNX. After rigid body refinement, an Rfree of 49.4 % was obtained. After calculation of a density modified map, the structure was rebuilt using TURBO-FRODO (Roussel A. et

Cambillau C. (1989) TURBO-FRODO. Silicon Graphics Geometry Partner Directory, Silicon Graphics, Mountain view, California). A maximum likelihood target (with a flat bulk solvent correction and no low resolution or sigma cutoff applied to the data) was used in the refinement protocol. Refinement of the model using simulated annealing torsion angle refinement and individual temperature factor refinement protocol was alternated with manual inspection and rebuilding of the model using TURBO-FRODO. After several cycles of refinement and manual rebuilding, most of the protein has been modeled for chain A, with only a few residues at the N- and C- termini being disordered. For chain B however, two substantial regions in addition, are disordered: residues 52 to 69, and residues 181:218. This latter stretch encompasses most of the helical insertion domain (Met169-Phe226), which appears to lack substantial intra-molecular contacts that might otherwise pin it into position. In addition to the protein chain, it was found that five additional residues are visible in the active site of chain A, and four are visible in the active site for chain B. Since at least some of these residues are clearly histidines, and the residues bind in the histidine binding pocket, it would seem that the His tag from nearby symmetry related molecules span the solvent channel and are bound in the catalytic site. It should be noted that the exact identities of the side chains of residues beyond 1000-1002 is open to question; indeed, the self-similarity of the His-tag means that it is quite likely that there are several independent binding modes, where the His-tag binds with modes related by displacing the tag 1 residue towards its N- or C- terminus. 121 solvent molecules were picked manually using a combination of sigma A weighted 2Fo-Fc and Fo-Fc maps.

Structure solution and refined statistics are reported in Table 3, contained in FIGURE 10. FIGURE 11 contains a list of the atomic coordinates of the subject polypeptide and other molecules contained in the crystal. FIGURE 12 to FIGURE 16 depict various features of the crystal structure and other properties of a subject polypeptide.

(e) Analysis of the X-ray Structure of the Subject Polypeptide

General Description of Structure

Like many other aminoacyl-tRNA synthetases, HisRS is active as a homodimer (FIGURE 13A). As with the *E. coli*, *S. aureus*, and *T. thermophilus* enzymes, the *E. faecalis* HisRS monomer contains three domains (FIGURE 13B); the catalytic domain common to class II synthetases, the C-terminal domain most likely involved in binding the tRNA anticodon stem-loop, and a third a-helical domain inserted between motifs 2 and 3 in the catalytic domain. The C-terminal domain is connected to the catalytic domain by an

extended chain. The N-terminal catalytic domain (Met1-Asp168, Leu227-Glu319) has an eight-stranded β-sheet, with the central six strands forming the anti-parallel ,a-sheet that is conserved among all class II synthetases. The front of the β-sheet appears to be mostly open to allow substrate entry, while the back is well protected by helices and flanking loops (FIGURE 13B). The C-terminal subclass-defining domain (Leu330-Lys420) has a mixed five-stranded β-sheet and four helices. The helical insertion domain (Met169-Phe226) in the HisRS homo-dimer is ordered in one monomer (molecule A) but disordered in the other monomer.

In the dimer, the C-terminal domain of one subunit makes interactions exclusively with the catalytic domain of the other subunit. The two HisRS molecules in the dimer interact in a side by-side fashion with their C-terminal domains swapped (FIGURE 13A). One part of the dimer interface is between the catalytic domain of one monomer and the C-terminal domain of the other monomer. This interface is mostly hydrophilic. The other part of the interface is more hydrophobic and includes structural elements from the N-terminal loop (Met1-Leu12) and a small interface (SI) motif (Phe43-Leu77). The SI motif, shown in magenta in FIGURE 13B, is present in all class IIa synthetases. The two SI motifs interact intimately in the HisRS dimer, and the interaction is likely important for the HisRS mechanism.

Superposition of all the Cα atoms of the backbone of the available HisRS structures demonstrates that the catalytic core is quite rigid, bit that the peripheral domains are capable of considerable motion with respect to this platform. In general, the structures superimpose very closely, with "iterative magic fit" as implemented is Swiss pdb viewer giving an r.m.s.d. of 1.39 Å over 412 atoms. There is movement in the C terminal domain and in the insertion domain. The C-terminal domains undergo rigid body rotations of up to 8-15° (see, e.g., FIGURE 14), and the insertion domain appears capable of even more significant motions. The positions of the SI motifs in all the reported structures also move slightly. Since the SI motif involves both the active site and the dimer interface, the observed conformational change may implicate a communicational path between the two active sites of the dimer.

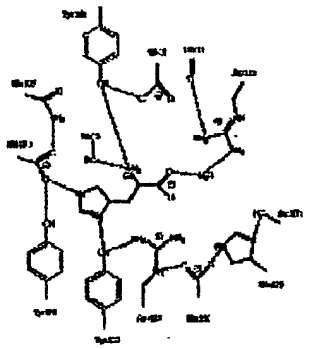
The most significant ligand-induced conformational changes occur in the histidine binding pocket (FIGURE 15). In the ligand bound structures, the binding pocket is a narrow cavity that is more than 20 Å deep. Atoms lining the pocket provide an intricate network of hydrogen bonding interactions as well as van der Waals contacts with the

substrate histidine. The changes seen in the apo *S. aureus* structure are centered at the HisA motif loop (257-RGLDYY-262) and the wide open pocket appears to require notable conformational changes to form a complementary binding pocket for histidine. In the *E. faecalis* structure, a polypeptide containing at least three consecutive histidine residues is found in binding pocket; presumably these residues correspond to the histidine tag. Although the tag was not cleaved, the C-terminus of symmetry related molecules can be found 18 and 21 Å way for the N-terminus of the peptides in the A and B monomers' binding sites respectively, a distance easily spanned by the fourteen to sixteen residues missing from the electron density map. An overlay of the *T. thermophilus* histidine bound structure with the *E. faecalis* structure shows some differences in the orientation of the side chain residues (FIGURE 15D).

Several important loops in the active site either become disordered or adopt very different conformations compared to their ligand-bound states. Such loops may comprising druggable regions. These include the histidine A motif (Arg257-Tyr262) that appears essential for substrate recognition, a loop (Gly52-Lys62) that seems to control the communication between the histidine and ATP binding sites, the motif 2 loop (Glu114-Arg120) that binds ATP, and the insertion domain that is likely to bind tRNA. These ligand-induced structural changes are supported by fluorescence experiments, which also suggest highly cooperative dynamics. A dynamic and cooperative active site is most likely necessary for the proper functioning of the histidyl-tRNA synthetase, and suggests a novel mechanism for improving charging fidelity.

Active Site and Other Druggable Regions

In the ligand-bound HisRS structures, the histidine-binding pocket seems to be optimized to utilize the hydrogen bonding capabilities of as well as shape and electrostatic complementarity to histidine. The histidine-binding pocket may comprise a druggable region. The active site residues, which may comprise a druggable region, appear to be highly conserved in HisRS (FIGURE 16). An alignment shows a high degree of sequence conservation along the length of the polypeptide chain amongst HisRS proteins from several pathogenic bacterial species (FIGURE 12). Table 4 describes the conserved active site residues for the histidine-ATP binding pocket. The HisRS specific peptides 259-RGLDYY and 287-GGRYNG (in *E. faecalis* and *S. aureus*; 285-GGRYDG in *T. thermophilus*, *E. coli*, *H. influenzae*, *P. aeruginosa* and *S. pneumoniae*) form a specific pocket where histidine is buried.

Table 4: Active site residues for HisRS in different species					
Binding Site Identifier	*E. faecalis*	*E. coli*	*T. thermophilus*	*S. aureus*	*Description of Binding Site*
Binding Site I: Histidine	P80 E81 T83 R114 G130 E132 R259 Y263 Y264 E270 M272 S282 Y290	P82 E83 T85 R113 G129 E131 R259 Y263 Y264 E270 V272 G280 Y288	P80 E81 T83 R112 N128 E130 R259 Y263 Y264 E270 H272 S280 Y288	P79 E80 T82 R112 G128 E130 R257 Y261 Y262 E268 M270 T281 Y289	 Figure of *T. thermophilus* histidine binding site from Aberg et al., 1997
Binding Site II: ATP	F126 E116 L123 I129carbonyl R114 R259	F125 E115 Y122 T12carbonyl R113 R259	F124 E114 Y121 V127carbonyl R112 R259	F124 E114 Y121 F127carbonyl R112 R257	ATP is selected over other purines. R259 is important for catalysis. R259 and R113 are unique to Syh since they replace metal ions coordinating the phosphates.
HisA motif	259RDLGYY264	259RDLGYY264	259RDLGYY264	257RDLGYY262	essential arginine in the HisA motif was observed to bind the R-phosphate and lies near the histidine carboxylate and is a likely catalytic residue, replacing the essential divalent metal ion (Mg2+) in other class II tRNA synthetases
HisB motif	287GGRYNGL293	285GGRYDGL291	285GGRYDGL291	286GGRYNGL292	Important when binding histidine

Hence, binding sites I and II, or subsets of the residues comprising them, may comprise a druggable region, as may the HisA and B motif regions or subsets of residues comprising them.

Known Inhibitors of Histidine tRNA synthetases

Many analogs of histidine have been tested for their properties as substrates or inhibitors of HisRS, leading to the elucidation of structure-activity relationships concerning configuration, importance of the carboxy and amino group, and the nature of the side chain.

Histidinol has been co-crystallized with ATP in *E. coli* HisRS (PDB ID 1KMN). ATP analogues have also been tested as substrates or inhibitors of HisRS.

Comparison to Other Histidine tRNA synthetases

Crystal structures of *Escherichia coli* HisRS in complex with histidyl-adenylate or with histidinol and ATP have been reported; as have *Thermus thermophilus* structures in complexes with histidine or with histidyl-adenylate. They all contain the class II and subclass IIa signature modules: the antiparallel β-sheet catalytic domain and the C-terminal anticodon-binding domain. A 60-residue insertion domain, in position to bind the tRNA acceptor stem, is visible in the *T. thermophilus* structures but is disordered in the *E. coli* structures. The HisA and HisB motifs interact intimately with the substrate histidine. The essential arginine in the HisA motif was observed to bind the R-phosphate and lies near the histidine carboxylate. The arginine is a likely catalytic residue, replacing the essential divalent metal ion (Mg2+) in other class II tRNA synthetases. Comparisons of the crystal structure of the apo *Staphylococcus aureus* histidyl-tRNA synthetase and ligand-bound structures reveal considerable conformational changes in the active site. These changes are ligand induced and presumed to occur in a highly cooperative fashion. The magnitude of the movement in HisRS is greater than any previously reported for tRNA synthetases.

Based in part on the structural information described above, in one aspect, the present invention is directed towards druggable regions of a subject polypeptide or other histidine tRNA synthetase comprising the majority of the amino acid residues contained in any of the above-described druggable regions. In another aspect, the present invention is directed toward an modulator or that interacts with an active or binding site of a histidine tRNA synthetase. In one embodiment, this site is binding site I of Table 4. In certain embodiments, the ADP/ATP binding site may be comprised of at least one of P80, E81, T83, R114, G130, E132, R259, Y263, Y264, E270, M272, S282, or Y290. In another embodiment, this site is binding site II of Table 4. In certain embodiments, the GMP binding site may be comprised of at least one of F126, E116, L123, I129carbonyl, R114, or R259. In another aspect, the present invention is directed towards an modulator that interacts with a loop of a histidine tRNA synthetase so as to modulate its movement, thereby modulating the activity of such enzyme. In certain embodiments, the loop is comprised of at least one residue selected from the group of loops consisting of: the HisA motif, the His B motif, the Gly52-Lys62 loop, and the insertion domain that is likely to bind tRNA.

EXAMPLE 17 Annotations

The functional annotation is arrived at by comparing the amino acid sequence of the ORF against all available ORFs in the NCBI database using BLAST. The closest match is selected to provide the probable function of the polypeptide having the sequence of SEQ ID NO: 2. Results of this comparison are described above and set forth in Table 2 of FIGURE 7.

The COGs database (Tatusov RL, Koonin EV, Lipman DJ. Science 1997; 278 (5338) 631-37) classifies proteins encoded in twenty-one completed genomes on the basis of sequence similarity. Members of the same Cluster of Orthologous Group, ("COG"), are expected to have the same or similar domain architecture and the same or substantially similar biological activity. The database may be used to predict the function of uncharacterised proteins through their homology to characterized proteins. The COGs database may be searched from NCBI's website (http://www.ncbi.nlm.nih.gov/COG/) to determine functional annotation descriptions, such as "information storage and processing" (translation, ribosomal structure and biogenesis, transcription, DNA replication, recombination and repair); "cellular processes" (cell division and chromosome partitioning, post-translational modification, protein turnover, chaperones, cell envelope biogenesis, outer membrane, cell motility and secretion, inorganic ion transport and metabolism, signal transduction mechanisms); or "metabolism" (energy production and conversion, carbohydrate transport and metabolism, amino acid transport and metabolism, nucleotide transport and metabolism, coenzyme metabolism, lipid metabolism). For certain polypeptides, there is no entry available. Results of this analysis are described above and set forth in Table 2 of FIGURE 7.

EXAMPLE 18 Essential Gene Analysis

SEQ ID NO: 2 is compared to a number of publicly available "essential genes" lists to determine whether that protein is encoded by an essential gene. An example of such a list is descended from a free release at the www.shigen.nig.ac.jp PEC (profiling of *E. coli* chromosome) site, http://www.shigen.nig.ac.jp/ecoli/pec/. The list is prepared as follows: a wildcard search for all genes in class "essential" yields the list of essential *E. coli* proteins encoded by essential genes, which number 230. These 230 hits are pruned by comparing against an NCBI *E. coli* genome. Only 216 of the 230 genes on the list are found in the

NCBI genome. These 216 are termed the essential-216-ecoli list. The essential-216-ecoli list is used to garner "essential" genes lists for other microbial genomes by blasting. For instance, formatting the 216-ecoli as a BLAST database, then BLASTing a genome (e.g. *S. aureus*) against it, elucidates all *S. aureus* genes with significant homology to a gene in the 216-essential list. SEQ ID NO: 2 is compared against the appropriate list and a match with a score of e^{-25} or better is considered an essential gene according to that list. In addition to the list described above, other lists of essential genes are publicly available or may be determined by methods disclosed publicly, and such lists and methods are considered in deciding whether a gene is essential. See, for example, Thanassi et al., Nucleic Acids Res 2002 Jul 15;30(14):3152-62; Forsyth et al., Mol Microbiol 2002 Mar;43(6):1387-400; Ji et al., Science 2001 Sep 21;293(5538):2266-9; Sassetti et al., Proc Natl Acad Sci U S A 2001 Oct 23;98(22):12712-7; Reich et al., J Bacteriol 1999 Aug;181(16):4961-8; Akerley et al., Proc Natl Acad Sci U S A 2002 Jan 22;99(2):966-71). Also, other methods are known in the art for determing whether a gene is essential, such as that disclosed in U.S. Patent Application No. 10/202,442 (filed July 24, 2002). The conclusion as to whether the gene encoding the amino acid sequence set forth in SEQ ID NO: 2 is essential is set forth in Table 2 of FIGURE 7.

EXAMPLE 19 PDB Analysis

SEQ ID NO: 2 is compared against the amino acid sequences in a database of proteins whose structures have been solved and released to the PDB (protein data bank). The identity/information about the top PDB homolog (most similar "hit", if any; a PDB entry is only considered a hit if the score is e^{-4} or better) is annotated, and the percent similarity and identity between SEQ ID NO: 2 and the closest hit is calculated, with both being indicated in Table 2 of FIGURE 7.

EXAMPLE 20 Virtual Genome Analysis

VGDB or VG is a queryable collection of microbial genome databases annotated with biophysical and protein information. The organisms present in VG include:

File	*GRAM*	*Species*	*Source*	*Genome file date*
ecoli.faa	G-	*Escherichia coli*	NCBI	November 18 1998
hpyl.faa	G-	*Helicobacter pylori*	NCBI	April 19 1999
paer.faa	G-	*Pseudomonas aeruginosa*	NCBI	September 22 2000

ctra.faa	G-	*Chlamydia trachomatis*	NCBI	December 22 1999
hinf.faa	G-	*Haemophilus influenzae*	NCBI	November 26 1999
nmen.faa	G-	*Neisseria meningitidis*	NCBI	December 28 2000
rpxx.faa	G-	*Rickettsia prowazekii*	NCBI	December 22 1999
bbur.faa	G-	*Borrelia burgdorferi*	NCBI	November 11 1998
bsub.faa	G+	*Bacillus subtilis*	NCBI	December 1 1999
staph.faa	G+	*Staphylococcus aureus*	TIGR	March 8 2001
spne.faa	G+	*Streptococcus pneumoniae*	TIGR	February 22 2001
mgen.faa	G+	*Mycoplasma genitalium*	NCBI	November 23 1999
efae.faa	G+	*Enterococcus faecalis*	TIGR	March 8 2001

The VGDB comprises 13 microbial genomes, annotated with biophysical information (pI, MW, etc), and a wealth of other information. These 13 organism genomes are stored in a single flatfile (the VGDB) against which PSI-blast queries can be done.

SEQ ID NO: 2 is queried against the VGDB to determine whether this sequence is found, conserved, in many microbial genomes. There are certain criteria that must be met for a positive hit to be returned (beyond the criteria inherent in a basic PSI-blast).

When an ORF is queried it may have a maximum of 13 VG-organism hits. A hit is classified as such as long as it matches the following criteria: Minimum Length (as percentage of query length): 75 *(Ensure hit protein is at least 75% as long as query)*; Maximum Length (as percentage of query length): 125 *(Ensure hit protein is no more than 125% as long as query)*; eVal:-10 *(Ensure hit has an e-Value of e-10 or better)*; Id%:>:25 *(Ensure hit protein has at least 25% identity to query)*. The e-Value is a standard parameter of BLAST sequence comparisons, and represents a measure of the similarity between two sequences based on the likelihood that any similarities between the two sequences could have occurred by random chance alone. The lower the e-Value, the less likely that the similarities could have occurred randomly and, generally, the more similar the two sequences are.

The organisms having an orthologue of the polypeptide having SEQ ID NO: 2 are listed in Table 2, shown in FIGURE 7.

EXAMPLE 21 Epitopic Regions

The three most likely epitopic regions of a polypeptide having SEQ ID NO: 2 are predicted using the semi-empirical method of Kolaskar and Tongaonkar (FEBS Letters 1990 v276 172-174), the software package called Protean (DNASTAR), or MacVectors's

Protein analysis tools (Accerlyrs). The antigenic propensity of each amino acid is calculated by the ratio between frequency of occurrence of amino acids in 169 antigenic determinants experimentally determined and the calculated frequency of occurrence of amino acids at the surface of protein. The results of these bioinformatics analyses are presented in Table 2, shown in FIGURE 7.

EQUIVALENTS

The present invention provides among other things, novel proteins, protein structures and protein-protein interactions. While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control. To the extent that any U.S. Provisional Patent Applications to which this patent application claims priority incorporate by reference another U.S. Provisional Patent Application, such other U.S. Provisional Patent Application is not incorporated by reference herein unless this patent application expressly incorporates by reference, or claims priorty to, such other U.S. Provisional Patent Application.

Also incorporated by reference in their entirety are any polynucleotide and polypeptide sequences which reference an accession number correlating to an entry in a public database, such as those maintained by The Institute for Genomic Research (TIGR) (www.tigr.org) and/or the National Center for Biotechnology Information (NCBI) (www.ncbi.nlm.nih.gov).

Also incorporated by reference are the following: WO 00/45168, WO 00/79238, WO 00/77712, EP 1047108, EP 1047107, WO 00/72004, WO 00/73787, WO00/67017, WO 00/48004, WO 01/48209, WO 00/45168, WO 00/45164, U.S.S.N. 09/720272; PCT/CA99/00640; U.S. Patent Application Nos: 10/097125 (filed March 12, 2002); 10/097193 (filed March 12, 2002); 10/202442 (filed July 24, 2002); 10/097194 (filed

March 12, 2002); 09/671817 (filed September 17, 2000); 09/965654 (filed September 27, 2001); 09/727812 (filed November 30, 2000); 60/370667 (filed April 8, 2002); a utility patent application entited "Methods and Appartuses for Purification" (filed September 18, 2002); U.S. Patent Numbers 6451591; 6254833; 6232114; 6229603; 6221612; 6214563; 6200762; 6171780; 6143492; 6124128; 6107477; D428157; 6063338; 6004808; 5985214; 5981200; 5928888; 5910287; 6248550; 6232114; 6229603; 6221612; 6214563; 6200762; 6197928; 6180411; 6171780; 6150176; 6140132; 6124128; 6107066; 6270988; 6077707; 6066476; 6063338; 6054321; 6054271; 6046925; 6031094; 6008378; 5998204; 5981200; 5955604; 5955453; 5948906; 5932474; 5925558; 5912137; 5910287; 5866548; 6214602; 5834436; 5777079; 5741657; 5693521; 5661035; 5625048; 5602258; 5552555; 5439797; 5374710; 5296703; 5283433; 5141627; 5134232; 5049673; 4806604; 4689432; 4603209; 6217873; 6174530; 6168784; 6271037; 6228654; 6184344; 6040133; 5910437; 5891993; 5854389; 5792664; 6248558; 6341256; 5854922; and 5866343.

Aberg, A., et al. (1997) Biochemistry, 36, 3084-3094; Arnez, J. G., et al. (1997) Proc. Natl Acad. Sci. USA, 94, 7144-7149; Arnez, J. G., et al. (1995) EMBO J. 14, 4143-4155; Francklyn, C., et al. (1990) Proc. Natl. Acad. Sci. U.S.A.87, 8655-8659; Francklyn, C., et al. (1992) Science 255,1121-1125; Freist W, et al. (1999) Biol Chem. 380, 623-46; Himeno, H., et al. (1989) Nucleic Acids Res. 19, 7855-7863; Nameki, N., et al. (1995) Nucleic Acid Res. 23, 389-394; Qiu, X., et al. (1999) Biochemistry, 38, 12296-12304; Steinberg, S., et al. (1993) Nucleic Acids Res. 21, 3011-3015; Xiayang Qiu, et al. (1999) Biochemistry 38, 12296-12304; Yan, W., et al. (1994) J. Biol. Chem. 269, 10022-10027.

We claim:

CLAIMS

1. A composition comprising an isolated, recombinant polypeptide, wherein the polypeptide comprises: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of *histidine tRNA synthetase* from *E. faecalis*; and wherein the polypeptide of (a), (b) or (c) is at least about 90% pure in a sample of the composition.

2. The composition of claim 1, wherein the polypeptide is at least about 95% pure as determined by gel electrophoresis.

3. The composition of claim 1, wherein the polypeptide is purified to essential homogeneity.

4. The composition of claim 1, wherein at least about two-thirds of the polypeptide in the sample is soluble.

5. The composition of claim 1, wherein the polypeptide is fused to at least one heterologous polypeptide that increases the solubility or stability of the polypeptide.

6. The composition of claim 1, which further comprises a matrix suitable for mass spectrometry.

7. The composition of claim 6, wherein the matrix is a nicotinic acid derivative or a cinnamic acid derivative.

8. A sample comprising an isolated, recombinant polypeptide, wherein the polypeptide comprises: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; and wherein the polypeptide of (a), (b) or (c) is labeled with a heavy atom.

9. The sample of claim 8, wherein the heavy atom is one of the following: cobalt, selenium, krypton, bromine, strontium, molybdenum, ruthenium, rhodium, palladium, silver, cadmium, tin, iodine, xenon, barium, lanthanum, cerium, praseodymium,

neodymium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium, lutetium, tantalum, tungsten, rhenium, osmium, iridium, platinum, gold, mercury, thallium, lead, thorium and uranium.

10. The sample of claim 8, wherein the polypeptide is labeled with seleno-methionine.

11. The sample of claim 8, further comprising a cryo-protectant.

12. The sample of claim 11, wherein the cryo-protectant is one of the following: methyl pentanediol, isopropanol, ethylene glycol, glycerol, formate, citrate, mineral oil and a low-molecular-weight polyethylene glycol.

13. A crystallized, recombinant polypeptide comprising: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; wherein the polypeptide of (a), (b) or (c) is in crystal form.

14. A crystallized complex comprising the crystallized, recombinant polypeptide of claim 13 and a co-factor, wherein the complex is in crystal form.

15. A crystallized complex comprising the crystallized, recombinant polypeptide of claim 13 and a small organic molecule, wherein the complex is in crystal form.

16. The crystallized, recombinant polypeptide of claim 13, which diffracts x-rays to a resolution of about 3.5 Å or better.

17. The crystallized, recombinant polypeptide of claim 13, wherein the polypeptide comprises at least one heavy atom label.

18. The crystallized, recombinant polypeptide of claim 17, wherein the polypeptide is labeled with seleno-methionine.

19. A method for designing a modulator for the prevention or treatment of *E. faecalis* related disease or disorder, comprising:

(a) providing a three-dimensional structure for a crystallized, recombinant polypeptide of claim 13;

(b) identifying a potential modulator for the prevention or treatment of *E. faecalis* related disease or disorder by reference to the three-dimensional structure;

(c) contacting a polypeptide of the composition of claim 1 or *E. faecalis* with the potential modulator; and

(d) assaying the activity of the polypeptide or determining the viability of *E. faecalis* after contact with the modulator, wherein a change in the activity of the polypeptide or the viability of *E. faecalis* indicates that the modulator may be useful for prevention or treatment of a *E. faecalis* related disease or disorder.

20. A sample comprising an isolated, recombinant polypeptide, wherein the polypeptide comprises: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; and wherein the polypeptide of (a), (b) or (c) is enriched in at least one NMR isotope.

21. The sample of claim 20, wherein the NMR isotope is one of the following: hydrogen-1 (^{1}H), hydrogen-2 (^{2}H), hydrogen-3 (^{3}H), phosphorous-31 (^{31}P), sodium-23 (^{23}Na), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), carbon-13 (^{13}C) and fluorine-19 (^{19}F).

22. The sample of claim 20, further comprising a deuterium lock solvent.

23. The sample of claim 22, wherein the deuterium lock solvent is one of the following: acetone (CD_3COCD_3), chloroform ($CDCl_3$), dichloro methane (CD_2Cl_2), methylnitrile (CD_3CN), benzene (C_6D_6), water (D_2O), diethylether ($(CD_3CD_2)_2O$), dimethylether ($(CD_3)_2O$), N,N-dimethylformamide ($(CD_3)_2NCDO$), dimethyl sulfoxide (CD_3SOCD_3), ethanol (CD_3CD_2OD), methanol (CD_3OD), tetrahydrofuran (C_4D_8O), toluene ($C_6D_5CD_3$), pyridine (C_5D_5N) and cyclohexane (C_6H_{12}).

24. The sample of claim 20, which is contained within an NMR tube.

25. A method for identifying small molecules that bind to a polypeptide of the composition of claim 1, comprising:

(a) generating a first NMR spectrum of an isotopically labeled polypeptide of the composition of claim 1;

(b) exposing the polypeptide to one or more small molecules;

(c) generating a second NMR spectrum of the polypeptide which has been exposed to one or more small molecules; and

(d) comparing the first and second spectra to determine differences between the first and the second spectra, wherein the differences are indicative of one or more small molecules that have bound to the polypeptide.

26. A host cell comprising a nucleic acid encoding a polypeptide comprising: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; wherein a culture of the host cell produces at least about 1 mg of the polypeptide per liter of culture and the polypeptide is at least about one-third soluble as measured by gel electrophoresis.

27. An isolated, recombinant polypeptide, comprising: (a) an amino acid sequence having at least about 90% identity with the amino acid sequence set forth in SEQ ID NO: 4; or (b) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; and wherein the polypeptide comprises one or more of the following amino acid residues at the specified position of the polypeptide: P80, E81, T83, R114, G130, E132, R259, Y263, Y264, E270, M272, S282, or Y290.

28. A method for obtaining structural information of a crystallized polypeptide, the method comprising:

(a) crystallizing a recombinant polypeptide, wherein the polypeptide comprises: (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; and wherein the crystallized polypeptide is capable of diffracting X-rays to a resolution of 3.5 Å or better; and

(b) analyzing the crystallized polypeptide by X-ray diffraction to determine the three-dimensional structure of at least a portion of the crystallized polypeptide.

29. The method of claim 28, wherein the three-dimensional structure of the portion of the crystallized polypeptide is determined to a resolution of 3.5 Å or better.

30. A method for identifying a druggable region of a polypeptide, the method comprising:

(a) obtaining crystals of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*, such that the three dimensional structure of the crystallized polypeptide may be determined to a resolution of 3.5 Å or better;

(b) determining the three dimensional structure of the crystallized polypeptide using X-ray diffraction; and

(c) identifying a druggable region of the crystallized polypeptide based on the three-dimensional structure of the crystallized polypeptide.

31. The method of claim 30, wherein the druggable region is an active site.

32. The method of claim 31, wherein the druggable region is on the surface of the polypeptide.

33. Crystalline histidine tRNA synthetase from *E. faecalis* comprising a crystal having unit cell dimenstions a = 76.434 Å, b = 112.876 Å, c = 125.792 Å, $\alpha = \beta = \gamma = 90°$ and space group $P2_12_12_1$.

34. A crystallized polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of *histidine tRNA synthetase* from *E. faecalis*; wherein the crystal has a $P2_12_12_1$ space group.

35. A crystallized polypeptide comprising a structure of a polypeptide that is defined by a substantial portion of the atomic coordinates set forth in FIGURE 11.

36. A method for determining the crystal structure of a homolog of a polypeptide, the method comprising:

(a) providing the three dimensional structure of a first crystallized polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of *histidine tRNA synthetase* from *E. faecalis*;

(b) obtaining crystals of a second polypeptide comprising an amino acid sequence that is at least 70% identical to the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4, such that the three dimensional structure of the second crystallized polypeptide may be determined to a resolution of 3.5 Å or better; and

(c) determining the three dimensional structure of the second crystallized polypeptide by x-ray crystallography based on the atomic coordinates of the three dimensional structure provided in step (a).

37. The method of claim 36, wherein the atomic coordinates for the second crystallized polypeptide have a root mean square deviation from the backbone atoms of the first polypeptide of not more than 1.5 Å for all backbone atoms shared in common with the first polypeptide and the second polypeptide.

38. A method for homology modeling a homolog of histidine tRNA synthetase from *E. faecalis*, comprising:

(a) aligning the amino acid sequence of a homolog of histidine tRNA synthetase from *E. faecalis* with an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and incorporating the sequence of the homolog of histidine tRNA synthetase from *E. faecalis* into a model of histidine tRNA synthetase from *E. faecalis* derived from structure coordinates as listed in FIGURE 11 to yield a preliminary model of the homolog of histidine tRNA synthetase from *E. faecalis*;

(b) subjecting the preliminary model to energy minimization to yield an energy minimized model;

(c) remodeling regions of the energy minimized model where stereochemistry restraints are violated to yield a final model of the homolog of histidine tRNA synthetase from *E. faecalis*.

39. A method for obtaining structural information about a molecule or a molecular complex of unknown structure comprising:

(a) crystallizing the molecule or molecular complex;

(b) generating an x-ray diffraction pattern from the crystallized molecule or molecular complex;

(c) applying at least a portion of the structure coordinates set forth in FIGURE 11 to the x-ray diffraction pattern to generate a three-dimensional electron density map of at least a portion of the molecule or molecular complex whose structure is unknown.

40. A method for attempting to make a crystallized complex comprising a polypeptide and a modulator having a molecular weight of less than 5 kDa, the method comprising:

(a) crystallizing a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; such that crystals of the crystallized polypeptide will diffract x-rays to a resolution of 5 Å or better; and

(b) soaking the crystals in a solution comprising a potential modulator having a molecular weight of less than 5 kDa.

41. A method for incorporating a potential modulator in a crystal of a polypeptide, comprising placing a crystal of histidine tRNA synthetase from *E. faecalis* having unit cell dimensions a = 76.434 Å, b = 112.876 Å, c = 125.792 Å, $\alpha = \beta = \gamma = 90°$ and space group $P2_12_12_1$, in a solution comprising the potential modulator.

42. A computer readable storage medium comprising digitally encoded structural data, wherein the data comprises structural coordinates as listed in FIGURE 11 for the backbone atoms of at least about six amino acid residues from a druggable region of histidine tRNA synthetase from *E. faecalis*.

43. A scalable three-dimensional configuration of points, at least a portion of the points derived from some or all of the structure coordinates as listed in FIGURE 11 for a plurality of amino acid residues from a druggable region of histidine tRNA synthetase from *E. faecalis*.

44. The scalable three-dimensional configuration of points of claim 43, wherein the structure coordinates as listed in FIGURE 11 for the backbone atoms of at least about five amino acid residues from a druggable region of histidine tRNA synthetase from *E. faecalis* are used to derive part or all of the portion of points.

45. The scalable three-dimensional configuration of points of claim 43, wherein the structure coordinates as listed in FIGURE 11 for the backbone and optionally the side chain atoms of at least about ten amino acid residues from a druggable region of histidine tRNA synthetase from *E. faecalis* are used to derive part or all of the portion of points.

46. The scalable three-dimensional configuration of points of claim 43, wherein the structure coordinates as listed in FIGURE 11 for the backbone atoms of at least about fifteen amino acid residues from a druggable region of histidine tRNA synthetase from *E. faecalis* are used to derive part or all of the portion of points.

47. The scalable three-dimensional configuration of points of claim 43, wherein substantially all of the points are derived from structure coordinates as listed in FIGURE 11.

48. The scalable three-dimensional configuration of points of claim 43, wherein the structure coordinates as listed in FIGURE 11 for the atoms of the amino acid residues from any of the above-described druggable regions of histidine tRNA synthetase from *E. faecalis* are used to derive part or all of the portion of points:

49. A scalable three-dimensional configuration of points, comprising points having a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in FIGURE 11 for the backbone atoms of at least five amino acid residues, wherein the five amino acid residues are from a druggable region of histidine tRNA synthetase from *E. faecalis*.

50. The scalable three-dimensional configuration of points of claim 49, wherein any point-to-point distance, calculated from the three dimensional coordinates as listed in FIGURE 11, between one of the backbone atoms for one of the five amino acid residues and another backbone atom of a different one of the five amino acid residues is not more than about 10 Å.

51. A scalable three-dimensional configuration of points comprising points having a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in FIGURE 11 for the atoms of the amino acid residues from any of the above-described druggable regions of histidine tRNA synthetase from *E. faecalis*:

52. A computer readable storage medium comprising digitally encoded structural data, wherein the data comprise the identity and three-dimensional coordinates as listed in FIGURE 11 for the atoms of the amino acid residues from any of the above-described druggable regions of histidine tRNA synthetase from *E. faecalis*:

53. A scalable three-dimensional configuration of points, wherein the points have a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in FIGURE 11 for the atoms of the amino acid residues from any of the above-described druggable regions of histidine tRNA synthetase from *E. faecalis*, wherein up to one amino acid residue in each of the regions may have a conservative substitution thereof.

54. A scalable three-dimensional configuration of points derived from a druggable region of a polypeptide, wherein the points have a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in FIGURE 11 for the backbone atoms of at least ten amino acid residues that participate in the intersubunit contacts of histidine tRNA synthetase from *E. faecalis*.

55. A computer-assisted method for identifying an inhibitor of the activity of histidine tRNA synthetase from *E. faecalis*, comprising:

(a) supplying a computer modeling application with a set of structure coordinates as listed in FIGURE 11 for the atoms of the amino acid residues from any of the above-described druggable regions of histidine tRNA synthetase from *E. faecalis* so as to define part or all of a molecule or complex;

(b) supplying the computer modeling application with a set of structure coordinates of a chemical entity; and

(c) determining whether the chemical entity is expected to bind to or interfere with the molecule or complex.

56. The method of claim 55, wherein determining whether the chemical entity is expected to bind to or interfere with the molecule or complex comprises performing a fitting operation between the chemical entity and a druggable region of the molecule or complex, followed by computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the druggable region.

57. The method of claim 55, further comprising screening a library of chemical entities.

58. A computer-assisted method for designing an inhibitor of histidine tRNA synthetase activity comprising:

(a) supplying a computer modeling application with a set of structure coordinates having a root mean square deviation of less than about 1.5 Å from the structure coordinates as listed in FIGURE 11 for the atoms of the amino acid residues from any of the above-described druggable regions of histidine tRNA synthetase from *E. faecalis* so as to define part or all of a molecule or complex;

(b) supplying the computer modeling application with a set of structure coordinates for a chemical entity;

(c) evaluating the potential binding interactions between the chemical entity and the molecule or complex;

(d) structurally modifying the chemical entity to yield a set of structure coordinates for a modified chemical entity; and

(e) determining whether the modified chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex, wherein binding to or interfering with the molecule or molecular complex is indicative of potential inhibition of histidine tRNA synthetase activity.

59. The method of claim 58, wherein determining whether the modified chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex comprises performing a fitting operation between the chemical entity and the molecule or complex, followed by computationally analyzing the results of the fitting operation to evaluate the association between the chemical entity and the molecule or complex.

60. The method of claim 58, wherein the set of structure coordinates for the chemical entity is obtained from a chemical library.

61. A computer-assisted method for designing an inhibitor of histidine tRNA synthetase activity *de novo* comprising:

(a) supplying a computer modeling application with a set of three-dimensional coordinates derived from the structure coordinates as listed in FIGURE 11 for the atoms of the amino acid residues from any of the above-described druggable regions of histidine tRNA synthetase from *E. faecalis* so as to define part or all of a molecule or complex;

(b) computationally building a chemical entity represented by a set of structure coordinates; and

(c) determining whether the chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex, wherein binding to or interfering with the molecule or complex is indicative of potential inhibition of histidine tRNA synthetase activity.

62. The method of claim 61, wherein determining whether the chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex comprises performing a fitting operation between the chemical entity and a druggable region of the molecule or complex, followed by computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the druggable region.

63. The method of any of claims 55, 58 or 61, further comprising supplying or synthesizing the potential inhibitor, then assaying the potential inhibitor to determine whether it inhibits histidine tRNA synthetase activity.

64. A method for identifying a potential modulator for the prevention or treatment of a *E. faecalis* related disease or disorder, the method comprising:

(a) providing the three dimensional structure of a crystallized polypeptide comprising: (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*;

(b) obtaining a potential modulator for the prevention or treatment of *E. faecalis* related disease or disorder based on the three dimensional structure of the crystallized polypeptide;

(c) contacting the potential modulator with a second polypeptide comprising: (i) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (ii) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (iii) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine

tRNA synthetase from *E. faecalis*; which second polypeptide may optionally be the same as the crystallized polypeptide; and

(d) assaying the activity of the second polypeptide, wherein a change in the activity of the second polypeptide indicates that the compound may be useful for prevention or treatment of a *E. faecalis* related disease or disorder.

65. A method for designing a candidate modulator for screening for inhibitors of a polypeptide, the method comprising:

(a) providing the three dimensional structure of a druggable region of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; and

(b) designing a candidate modulator based on the three dimensional structure of the druggable region of the polypeptide.

66. A method for identifying a potential modulator of a polypeptide from a database, the method comprising:

(a) providing the three-dimensional coordinates for a plurality of the amino acids of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*;

(b) identifying a druggable region of the polypeptide; and

(c) selecting from a database at least one potential modulator comprising three dimensional coordinates which indicate that the modulator may bind or interfere with the druggable region.

67. The method of claim 66, wherein the modulator is a small molecule.

68. A method for preparing a potential modulator of a druggable region contained in a polypeptide, the method comprising:

(a) using the atomic coordinates for the backbone atoms of at least about six amino acid residues from a polypeptide of SEQ ID NO: 4, with a ± a root mean square deviation from the backbone atoms of the amino acid residues of not more than 1.5 Å, to generate one or more three-dimensional structures of a molecule comprising a druggable region from the polypeptide;

(b) employing one or more of the three dimensional structures of the molecule to design or select a potential modulator of the druggable region; and

(c) synthesizing or obtaining the modulator.

69. An apparatus for determining whether a compound is a potential modulator of a polypeptide, the apparatus comprising:

(a) a memory that comprises:

(i) the three dimensional coordinates and identities of at least about fifteen atoms from a druggable region of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*;

(ii) executable instructions; and

(b) a processor that is capable of executing instructions to:

(i) receive three-dimensional structural information for a candidate modulator;

(ii) determine if the three-dimensional structure of the candidate modulator is complementary to the three dimensional coordinates of the atoms from the druggable region; and

(iii) output the results of the determination.

70. A method for making an inhibitor of histidine tRNA synthetase activity, the method comprising chemically or enzymatically synthesizing a chemical entity to yield an

inhibitor of histidine tRNA synthetase activity, the chemical entity having been identified during a computer-assisted process comprising supplying a computer modeling application with a set of structure coordinates of a molecule or complex, the molecule or complex comprising at least a portion of at least one druggable region from histidine tRNA synthetase from *E. faecalis*; supplying the computer modeling application with a set of structure coordinates of a chemical entity; and determining whether the chemical entity is expected to bind or to interfere with the molecule or complex at a druggable region, wherein binding to or interfering with the molecule or complex is indicative of potential inhibition of histidine tRNA synthetase activity.

71. A computer readable storage medium comprising digitally encoded data, wherein the data comprises structural coordinates for a druggable region that is structurally homologous to the structure coordinates as listed in FIGURE 11 for a druggable region of histidine tRNA synthetase from *E. faecalis*.

72. A computer readable storage medium comprising digitally encoded structural data, wherein the data comprise a majority of the three-dimensional structure coordinates as listed in FIGURE 11.

73. The computer readable storage medium of claim 72, further comprising the identity of the atoms for the majority of the three-dimensional structure coordinates as listed in FIGURE 11.

74. The computer readable storage medium of claim 72, wherein the data comprise substantially all of the three-dimensional structure coordinates as listed in FIGURE 11.

FIGURE 1

SEQ ID NO: 1

ATGAGTTATCAAAAACCAAAAGGAACAAACGATATTTTGCCAGGAACTTCTGA
AAAATGGCAATTTGTGGAAGAAACAGCTCGTTTGATTTTTAAAGATTATCAATACCAAG
AAATCAGAACCCCGATTTTTGAACATTATGAAGTAATATCTCGCAGTGTTGGCGATACC
ACAGATATTGTTTCAAAAGAAATGTATGATTTTTATGATAAAGGAGACCGTCACGTGAC
GCTACGTCCTGAGGGGACAGCGCCAATTGTTCGGGCCTTCGTTGAAAATAAATTATATG
GTCCGGAATATACGAAACCATATAAAACCTATTACATGGGGCCGATGTTCCGCTATGA
ACGCCCACAAGCTGGTCGTTTGCGTCAATTCCATCAAATTGGTGTGGAAGCATTTGGTA
GTGAAAACCCAGCATTGGATGTTGAAATCATGGCTATGGCTTTGGACTTCTTCAAACAA
TTAGGCATCCAACAAATCAAATTAGTTATTAATTCCTTGGGGGATAAAGAAACACGTG
CTACGTACCGTCAAGCATTAATCGATTATTTAGAGCCCCATATGGCAGAATTAAGCGAG
GATTCACAACGTCGCTTACACGAAAACCCATTGCGGGTGTTAGACAGCAAAGATAAAA
AAGACAAGGTGATTGTCGCAGAAGCGCCCTCCATTTTGGATTATTTAAATGAACCATCT
AAAGCACATTTTGAAGCAGTAACTGATATGTTAGATTTACTAGAAATTCCTTATGAAAT
TGATAGTAATATGGTTCGTGGCCTGGATTATTATACACACACAATTTTTGAAATTATGA
GTGAAGCGCCTAAAATGGGTGCGCAATCAACTATTTGTGCAGGAGGCCGATACAATGG
TTTAGTTGAAGAATTAGGCGGCCCAGACACACCAGGTTTTGGTTTTGGTATGGGCATTG
AGCGAGTGTTGTTAACAATGGAAGCTGAAGAAGTTGTGATTCCAGCGTTATCTGAATTA
GACGCATATGTGGTTGGGATTGGTTCAGACACCAACGTCGCAGCTTTGCAACTTGTTCA
AAGCATTCGTAACTTTGGTTTCTCAGCTGATCGTGATTACATGAATCGCAAACCAAAAG
CGCAATTTAAAACGGCCGATAAATTACAAGCAAAATTAGTTTTAACAATCGGTGAAAA
TGAATTGAATGAAGGCATTGTCAACGTAAAATCAATGGCAACACGCGAAGAAAAAGCC
TTCCCGTTAAGTGCTATTCATGATTCATTTGATGAAGTGTATGACGAAATGATGACAAA
AATGATTGAAGAATGA

FIGURE 2

SEQ ID NO: 2

MSYQKPKGTNDILPGTSEKWQFVEETARLIFKDYQYQEIRTPIFEHYEVISRSVGDTT
DIVSKEMYDFYDKGDRHVTLRPEGTAPIVRAFVENKLYGPEYTKPYKTYYMGPMFRYERP
QAGRLRQFHQIGVEAFGSENPALDVEIMAMALDFFKQLGIQQIKLVINSLGDKETRATYRQ
ALIDYLEPHMAELSEDSQRRLHENPLRVLDSKDKKDKVIVAEAPSILDYLNEPSKAHFEAVT
DMLDLLEIPYEIDSNMVRGLDYYTHTIFEIMSEAPKMGAQSTICAGGRYNGLVEELGGPDTP
GFGFGMGIERVLLTMEAEEVVIPALSELDAYVVGIGSDTNVAALQLVQSIRNFGFSADRDY
MNRKPKAQFKTADKLQAKLVLTIGENELNEGIVNVKSMATREEKAFPLSAIHDSFDEVYDE
MMTKMIEE

FIGURE 3

SEQ ID NO: 3

ATGAGTTATCAAAAACCAAAAGGAACAAACGATATTTTGCCAGGAACTTCTGA
AAAATGGCAATTTGTGGAAGAAACAGCTCGTTTGATTTTTAAAGATTATCAATACCAAG
AAATCAGAACCCCGATTTTTGAACATTATGAAGTAATATCTCGCAGTGTTGGCGATACC
ACAGATATTGTTTCAAAAGAAATGTATGATTTTTATGATAAAGGAGACCGTCACGTGAC
GCTACGTCCTGAGGGGACAGCGCCAATTGTTCGGGCCTTCGTTGAAAATAAATTATATG
GTCCGGGATATACGAAACCATATAAAACCTATTACGTGGGGCCGATGTTCCGCTATGA
ACGCCCACAAGCTGGTCGTTTGCGTCAATTCCATCAAATTGGTGTGGAAGCGTTTGGTA
GTGGAAACCCACCATTGGATGTTGAAATCATGGCTATGGCTTTGGACTTCTTCAAACAA
TTAGGCATCCAACAAATCAAATTAATTATTAATTCCTTGGGGGATAAAGAAACACGTG
CTACGTACCGTCCAGCATTAATCGATTATTTAGAGCCCCATATGGCAGAATTAAGCGAG
GATTCACAACGTCGCTTACACGAAAACCCATTGCGGGTGTTAGACAGCAAAGATAAAA
AAGACAAGGTGATTGTCGCAGAAGCGCCCTCCATTTTGGATTATTTAAATGAACCATCT
AAAGCACATTTTGAAGCAGTAACTGATATGTTAGATTTACTAGAAATTCCTTATGAAAT
TGATAGTAATATGGTTCGTGGCCTGGATTATTATACACACACAATTTTTGAAATTAGGA
GTGAAGCGCTTAAAATGGGTGCGCAATCAACTATTTGTGCAGGAGGCCGATACAATGG
TTTAGTTGAAGAATTAGGCGGCCCAGACACACCAGGTTTTGGTTTTGGTATGGGCATTG
AGCGAGTGTTGTTAACAATGGAAGCTGAAGAAGTTGTGATTCCAGCGTTATCTGAATTA
GACGCATATGTGGTTGGGATTGGTTCAGACACCAACGTCGCAGCTTTGCAACTTGTTCA
AAGCATTCGTAACTTTGGTTTCTCAGCTGATCGTGATTACATGAATCGCAAACCAAAAG
CGCAATTTAAAACGGCCGATAAATTACAAGCAAAATTAGTTTTAACAATCGGTGAAAA
TGAATTGAATGAAGGCATTGTCAACGTAAAATCAATGGCAACACGCGAAGAAAAAGCC
TTCCCGTTAAGTGCTATTCATGATTCATTTGATGAAGTGTATGACGAAATGATGACAAA
AATGATTGAAGAATGA

FIGURE 4

SEQ ID NO: 4

MSYQKPKGTNDILPGTSEKWQFVEETARLIFKDYQYQEIRTPIFEHYEVISRSVGDTT
DIVSKEMYDFYDKGDRHVTLRPEGTAPIVRAFVENKLYGPGYTKPYKTYYVGPMFRYERP
QAGRLRQFHQIGVEAFGSGNPPLDVEIMAMALDFFKQLGIQQIKLIINSLGDKETRATYRPA
LIDYLEPHMAELSEDSQRRLHENPLRVLDSKDKKDKVIVAEAPSILDYLNEPSKAHFEAVTD
MLDLLEIPYEIDSNMVRGLDYYTHTIFEIRSEALKMGAQSTICAGGRYNGLVEELGGPDTPG
FGFGMGIERVLLTMEAEEVVIPALSELDAYVVGIGSDTNVAALQLVQSIRNFGFSADRDYM
NRKPKAQFKTADKLQAKLVLTIGENELNEGIVNVKSMATREEKAFPLSAIHDSFDEVYDEM
MTKMIEE

FIGURE 5

SEQ ID NO: 5

Forward PCR Primer

CGCGGGGTACCATGAGTTATCAAAAACCAAAAGG

SEQ ID NO: 6

Reverse PCR Primer

GCGCGGATCCTTCAATCATTTTTGTCATCATTTC

FIGURE 6

TABLE 1: Amino Acid and Nucleic Acid Properties

Melting temperature (°C) of SEQ ID NO: 5 (forward PCR primer)	60
Restriction enzyme for SEQ ID NO: 5 (forward PCR primer)	KpnI
Melting temperature (°C) of SEQ ID NO: 6 (reverse PCR primer)	60
Restriction enzyme for SEQ ID NO: 6 (reverse PCR primer)	BamHI
Number of nucleic acid residues in SEQ ID NO: 1	1302
Number of amino acid residues in SEQ ID NO: 2	433
Number of different nucleic acid residues between SEQ ID NO: 1 and SEQ ID NO: 3	9
Number of different amino acid residues between SEQ ID NO: 2 and SEQ ID NO: 4	8
Calculated molecular weight of SEQ ID NO: 2 polypeptide (kDa)	49.273
Calculated pI of SEQ ID NO: 2 polypeptide	4.5
Solubility of SEQ ID NO: 4 polypeptide, determined as described in EXAMPLE 2 (with the His tag at the N-terminus)	Approaching 100%
Solubility of SEQ ID NO: 4 polypeptide, determined as described in EXAMPLE 2 (with the His tag at the C-terminus)	Approaching 100%
Amount of purified polypeptide having SEQ ID NO: 4, prepared and purified as described in EXAMPLE 8 (mg/L of culture)	31.03
Amount of purified polypeptide having SEQ ID NO: 4 soluble in buffer, as described in EXAMPLE 8 (mg/ml of buffer)	21.40
Z-score for the peptide fingerprint mapping analysis, determined as described in EXAMPLE 9	2.41
Number of matched peptides in the peptide fingerprint mapping analysis, determined as described in EXAMPLE 9	14
Minimum sequence coverage in the peptide fingerprint mapping analysis, determined as described in EXAMPLE 9	31%
Calculated molecular weight of SEQ ID NO: 2 polypeptide (Da), determined as described in EXAMPLE 10	51089
Experimental molecular weight of SEQ ID NO: 2 polypeptide (Da), determined as described in EXAMPLE 10	51031

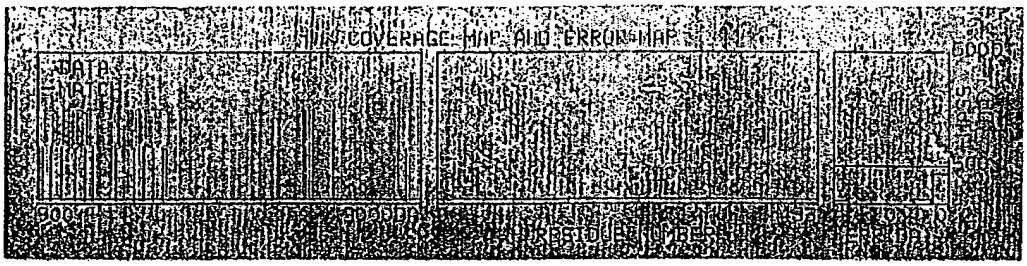
FIGURE 7

TABLE 2: Bioinformatic Analyses

Protein annotation and gene designation, if any	histidine tRNA synthetase, *hisS*
COG Category	Translation, ribosomal structure and biogenesis
COG ID Number	COG0124
Is SEQ ID NO: 2 classified as an essential gene?	yes
Most closely related protein from PDB	Histidyl-tRNA Synthetase, (1qe0)
Source organism for closest PDB protein	*Staphylococcus aureus*
e-value for closest PDB Protein	1.00E-118
% Identity between SEQ ID NO: 2 and the closest protein from PDB	48
% Positives between SEQ ID NO: 2 and the closest protein from PDB	66
Number of Protein Hits in the VGDB	11
Number of Microorganisms having VGDB Hits	11
Microorganisms having VGDB Hits[1]	ecoli nmen saur rpro efae ctra hinf spne bsub paer mgen
First predicted epitopic region of SEQ ID NO: 2: rank score, amino acid residue numbers; amino acid sequence	1.201,343->353, SEQ ID NO:7 NVAALQLVQSI
Second predicted epitopic region of SEQ ID NO: 2: rank score, amino acid residue numbers; amino acid sequence	1.187,321->339, SEQ ID NO:8 EEVVIPALSELDAYVVGIG
Third predicted epitopic region of SEQ ID NO: 2: rank score, amino acid residue numbers; amino acid sequence	1.163,378->387, SEQ ID NO:9 KLQAKLVLTI

[1]Organisms are abbreviated as follows: ecoli = *Eschericia coli*; hpyl = *Helicobacter pylori*; paer = *Pseudomonas aeruginosa*; ctra = *Chlaydia trachomatis*; hinf = *Haemophilus influenzae*; nmen = *Neisseria meningitidis*; rpxx = *Rickettsia prowazekii*; bbur = *Borrelia burgdorferi*; bsub = *Bacillus subtilis*; staph = *Staphylococcus aureus*; spne = *Streptococcus pneumoniae*; mgen = *Mycoplasma genitalium*; efae = *Enterococcus faecalis*.

FIGURE 8



Measured Mass(M)	Avg/ Mono	Computed Mass	Error (Da)	Residues Start	To	Missed Cut	Peptide sequence
912.604	M	912.409	0.195	355	362	0	NFGFSADR
926.742	M	926.554	0.188	155	162	0	QLGIQQIK
975.659	M	975.488	0.171	115	122	0	YERPQAGR
1033.729	M	1033.578	0.151	199	206	1	RLHENPLR
1113.659	M	1113.509	0.151	33	40	0	DYQYQEIR
1164.687	M	1164.509	0.178	106	114	0	TYYMGPHFR
1164.687	M	1164.556	0.131	20	28	0	MQFVEETAR
1207.709	M	1207.543	0.166	278	289	0	MGAQSTICAGGR
1343.887	M	1343.740	0.147	163	174	1	LVINSLGDKETR
1437.725	M	1437.586	0.139	64	74	1	EHYDFYDKGDR
1489.896	M	1489.756	0.140	41	52	0	TPIFEHYEVISR
1545.024	M	1544.878	0.146	75	88	0	HVTLRPEGTAPIVR
1591.828	M	1591.683	0.145	355	367	1	NFGFSADRDYHNR
1614.981	M	1614.840	0.142	29	40	1	LIFKDYQYQEIR
2920.241	M	2920.397	-0.156	235	259	0	AHFEAVTDHLDLLEIPYEIDSNHVR

FIGURE 9

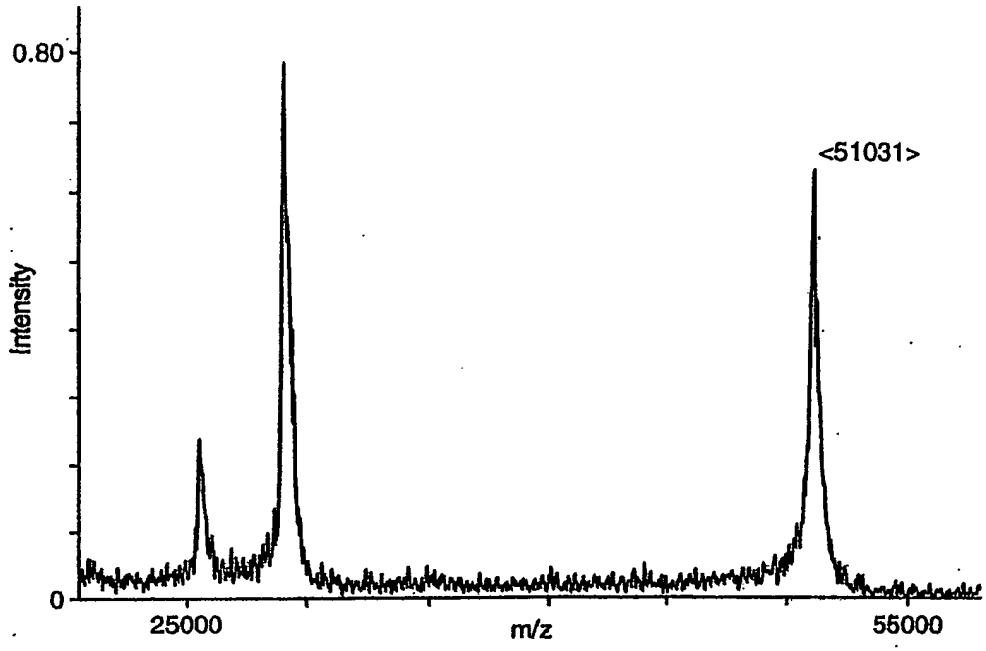


FIGURE 10

TABLE 3: X-ray Structure Data

(a) Data Collection	
Wavelength	1.0
Space group	$P2_12_12_1$
Unit cell dimensions	a = 76.434 Å b = 122.876 Å c = 125.792 Å; α = β = γ = 90°
Resolution range (Å)	20 - 2.3
Completeness (%)[a,b]	94.2(89.6)
I/σI	23(2.7)
R_{merge}	5.1(30.8)
Number of reflections: Total	314403
Unique	50355
(b) Structure Refinement	
R_{cryst}[d]	27.3
R_{free}	23.4
Number of atoms	
protein	6315
solvent	133
Average B-factors	
protein (Å^2)	57.9
solvent (Å^2)	52.6
R.M.S. Deviations from ideal	
Bond (Å)	0.007
Angle (°)	1.28

[a]Number in parentheses is the statistic for highest resolution shell.
[b]$I \geq \sigma I$
[c]$R_{sym} = \Sigma_h(\Sigma_j | I_{j,h} - < I_h > | / \Sigma I_{j,h})$, where h = set of Miller indices and j = set of observations of reflection h.
[d]$R_{cryst} = \Sigma_{hkl} | F_o - F_c | / \Sigma_{hkl} | F_o |$

FIGURE 11

```
ATOM      1  CB  THR A   9      82.065 149.640  59.961  1.00 68.18      A    C
ATOM      2  OG1 THR A   9      81.103 150.585  60.460  1.00 71.65      A    O
ATOM      3  CG2 THR A   9      83.371 149.794  60.749  1.00 66.04      A    C
ATOM      4  C   THR A   9      80.947 149.889  57.751  1.00 64.05      A    C
ATOM      5  O   THR A   9      80.020 150.589  58.164  1.00 63.15      A    O
ATOM      6  N   THR A   9      82.982 151.211  58.232  1.00 67.94      A    N
ATOM      7  CA  THR A   9      82.303 149.899  58.454  1.00 66.43      A    C
ATOM      8  N   ASN A  10      80.834 149.103  56.686  1.00 61.00      A    N
ATOM      9  CA  ASN A  10      79.577 149.019  55.958  1.00 57.40      A    C
ATOM     10  CB  ASN A  10      79.837 148.810  54.473  1.00 61.29      A    C
ATOM     11  CG  ASN A  10      80.243 150.086  53.774  1.00 64.80      A    C
ATOM     12  OD1 ASN A  10      81.290 150.663  54.063  1.00 67.11      A    O
ATOM     13  ND2 ASN A  10      79.405 150.541  52.851  1.00 66.47      A    N
ATOM     14  C   ASN A  10      78.706 147.893  56.482  1.00 53.96      A    C
ATOM     15  O   ASN A  10      77.916 147.319  55.738  1.00 53.22      A    O
ATOM     16  N   ASP A  11      78.860 147.579  57.766  1.00 49.07      A    N
ATOM     17  CA  ASP A  11      78.083 146.523  58.393  1.00 44.34      A    C
ATOM     18  CB  ASP A  11      78.794 145.982  59.635  1.00 44.30      A    C
ATOM     19  CG  ASP A  11      80.239 145.633  59.378  1.00 44.73      A    C
ATOM     20  OD1 ASP A  11      80.503 144.807  58.489  1.00 48.60      A    O
ATOM     21  OD2 ASP A  11      81.117 146.183  60.070  1.00 45.61      A    O
ATOM     22  C   ASP A  11      76.737 147.078  58.830  1.00 41.76      A    C
ATOM     23  O   ASP A  11      76.612 148.269  59.118  1.00 39.58      A    O
ATOM     24  N   ILE A  12      75.740 146.206  58.882  1.00 37.14      A    N
ATOM     25  CA  ILE A  12      74.409 146.588  59.323  1.00 36.54      A    C
ATOM     26  CB  ILE A  12      73.358 146.099  58.302  1.00 36.24      A    C
ATOM     27  CG2 ILE A  12      71.939 146.424  58.784  1.00 36.81      A    C
ATOM     28  CG1 ILE A  12      73.636 146.792  56.957  1.00 38.34      A    C
ATOM     29  CD1 ILE A  12      72.892 146.217  55.784  1.00 39.91      A    C
ATOM     30  C   ILE A  12      74.270 145.936  60.706  1.00 35.40      A    C
ATOM     31  O   ILE A  12      74.127 144.721  60.836  1.00 34.70      A    O
ATOM     32  N   LEU A  13      74.345 146.772  61.735  1.00 35.22      A    N
ATOM     33  CA  LEU A  13      74.316 146.341  63.135  1.00 35.02      A    C
ATOM     34  CB  LEU A  13      75.269 147.235  63.944  1.00 32.45      A    C
ATOM     35  CG  LEU A  13      76.664 147.353  63.339  1.00 32.19      A    C
ATOM     36  CD1 LEU A  13      77.474 148.420  64.054  1.00 30.72      A    C
ATOM     37  CD2 LEU A  13      77.328 145.998  63.411  1.00 30.95      A    C
ATOM     38  C   LEU A  13      72.968 146.356  63.834  1.00 35.24      A    C
ATOM     39  O   LEU A  13      72.009 146.946  63.352  1.00 33.73      A    O
ATOM     40  N   PRO A  14      72.886 145.692  64.996  1.00 38.29      A    N
ATOM     41  CD  PRO A  14      73.825 144.685  65.531  1.00 38.32      A    C
ATOM     42  CA  PRO A  14      71.624 145.676  65.739  1.00 40.38      A    C
ATOM     43  CB  PRO A  14      71.991 144.918  67.005  1.00 39.68      A    C
ATOM     44  CG  PRO A  14      72.937 143.870  66.474  1.00 37.76      A    C
ATOM     45  C   PRO A  14      71.234 147.125  66.008  1.00 42.45      A    C
ATOM     46  O   PRO A  14      72.066 147.925  66.439  1.00 43.56      A    O
ATOM     47  N   GLY A  15      69.980 147.474  65.734  1.00 43.90      A    N
ATOM     48  CA  GLY A  15      69.547 148.848  65.939  1.00 44.20      A    C
ATOM     49  C   GLY A  15      69.144 149.460  64.608  1.00 46.63      A    C
ATOM     50  O   GLY A  15      68.249 150.310  64.540  1.00 48.41      A    O
ATOM     51  N   THR A  16      69.817 149.053  63.536  1.00 43.84      A    N
ATOM     52  CA  THR A  16      69.445 149.557  62.234  1.00 42.13      A    C
ATOM     53  CB  THR A  16      70.608 150.303  61.522  1.00 42.92      A    C
ATOM     54  OG1 THR A  16      71.442 149.367  60.845  1.00 48.08      A    O
ATOM     55  CG2 THR A  16      71.445 151.084  62.530  1.00 42.75      A    C
ATOM     56  C   THR A  16      69.009 148.357  61.411  1.00 39.21      A    C
ATOM     57  O   THR A  16      68.188 148.481  60.499  1.00 38.90      A    O
ATOM     58  N   SER A  17      69.527 147.184  61.754  1.00 36.19      A    N
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FIGURE 11-11

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ATOM     59  CA  SER A  17      69.164 145.996  61.002  1.00 36.72      A    C
ATOM     60  CB  SER A  17      69.946 144.765  61.487  1.00 35.11      A    C
ATOM     61  OG  SER A  17      69.534 144.336  62.762  1.00 38.23      A    O
ATOM     62  C   SER A  17      67.661 145.765  61.097  1.00 35.40      A    C
ATOM     63  O   SER A  17      67.061 145.196  60.184  1.00 34.17      A    O
ATOM     64  N   GLU A  18      67.052 146.230  62.189  1.00 35.27      A    N
ATOM     65  CA  GLU A  18      65.608 146.087  62.373  1.00 35.54      A    C
ATOM     66  CB  GLU A  18      65.171 146.495  63.787  1.00 39.03      A    C
ATOM     67  CG  GLU A  18      65.560 145.507  64.856  1.00 47.64      A    C
ATOM     68  CD  GLU A  18      67.057 145.517  65.135  1.00 52.65      A    C
ATOM     69  OE1 GLU A  18      67.550 144.532  65.742  1.00 52.19      A    O
ATOM     70  OE2 GLU A  18      67.726 146.515  64.756  1.00 52.83      A    O
ATOM     71  C   GLU A  18      64.861 146.950  61.368  1.00 32.37      A    C
ATOM     72  O   GLU A  18      63.743 146.630  60.985  1.00 32.84      A    O
ATOM     73  N   LYS A  19      65.468 148.056  60.960  1.00 29.45      A    N
ATOM     74  CA  LYS A  19      64.835 148.926  59.987  1.00 29.61      A    C
ATOM     75  CB  LYS A  19      65.597 150.244  59.882  1.00 32.28      A    C
ATOM     76  CG  LYS A  19      65.627 150.998  61.219  1.00 37.74      A    C
ATOM     77  CD  LYS A  19      66.337 152.329  61.128  1.00 38.04      A    C
ATOM     78  CE  LYS A  19      66.329 153.024  62.480  1.00 38.26      A    C
ATOM     79  NZ  LYS A  19      66.731 154.450  62.353  1.00 42.24      A    N
ATOM     80  C   LYS A  19      64.810 148.201  58.653  1.00 30.98      A    C
ATOM     81  O   LYS A  19      63.779 148.171  57.970  1.00 31.46      A    O
ATOM     82  N   TRP A  20      65.942 147.602  58.294  1.00 27.27      A    N
ATOM     83  CA  TRP A  20      66.024 146.855  57.063  1.00 28.18      A    C
ATOM     84  CB  TRP A  20      67.392 146.195  56.919  1.00 28.59      A    C
ATOM     85  CG  TRP A  20      68.451 147.159  56.531  1.00 28.84      A    C
ATOM     86  CD2 TRP A  20      69.066 147.274  55.251  1.00 28.72      A    C
ATOM     87  CE2 TRP A  20      69.951 148.363  55.316  1.00 29.99      A    C
ATOM     88  CE3 TRP A  20      68.947 146.567  54.047  1.00 27.90      A    C
ATOM     89  CD1 TRP A  20      68.969 148.142  57.296  1.00 26.65      A    C
ATOM     90  NE1 TRP A  20      69.869 148.872  56.581  1.00 28.97      A    N
ATOM     91  CZ2 TRP A  20      70.728 148.774  54.221  1.00 31.05      A    C
ATOM     92  CZ3 TRP A  20      69.718 146.972  52.954  1.00 29.88      A    C
ATOM     93  CH2 TRP A  20      70.599 148.069  53.053  1.00 28.23      A    C
ATOM     94  C   TRP A  20      64.950 145.790  57.089  1.00 30.28      A    C
ATOM     95  O   TRP A  20      64.186 145.655  56.137  1.00 30.38      A    O
ATOM     96  N   GLN A  21      64.889 145.039  58.187  1.00 31.70      A    N
ATOM     97  CA  GLN A  21      63.897 143.980  58.329  1.00 31.66      A    C
ATOM     98  CB  GLN A  21      63.975 143.356  59.716  1.00 33.15      A    C
ATOM     99  CG  GLN A  21      65.057 142.295  59.876  1.00 36.22      A    C
ATOM    100  CD  GLN A  21      65.510 142.162  61.321  1.00 36.21      A    C
ATOM    101  OE1 GLN A  21      64.729 142.376  62.244  1.00 36.03      A    O
ATOM    102  NE2 GLN A  21      66.773 141.805  61.521  1.00 36.94      A    N
ATOM    103  C   GLN A  21      62.479 144.471  58.102  1.00 31.48      A    C
ATOM    104  O   GLN A  21      61.693 143.815  57.433  1.00 31.20      A    O
ATOM    105  N   PHE A  22      62.152 145.621  58.668  1.00 30.77      A    N
ATOM    106  CA  PHE A  22      60.818 146.162  58.525  1.00 29.48      A    C
ATOM    107  CB  PHE A  22      60.655 147.384  59.420  1.00 28.47      A    C
ATOM    108  CG  PHE A  22      59.354 148.105  59.228  1.00 30.37      A    C
ATOM    109  CD1 PHE A  22      58.150 147.523  59.618  1.00 31.57      A    C
ATOM    110  CD2 PHE A  22      59.329 149.365  58.667  1.00 29.20      A    C
ATOM    111  CE1 PHE A  22      56.940 148.191  59.453  1.00 27.20      A    C
ATOM    112  CE2 PHE A  22      58.115 150.045  58.498  1.00 31.63      A    C
ATOM    113  CZ  PHE A  22      56.923 149.448  58.897  1.00 27.64      A    C
ATOM    114  C   PHE A  22      60.537 146.541  57.071  1.00 31.86      A    C
ATOM    115  O   PHE A  22      59.414 146.385  56.589  1.00 33.16      A    O
ATOM    116  N   VAL A  23      61.542 147.059  56.374  1.00 31.48      A    N
ATOM    117  CA  VAL A  23      61.344 147.435  54.983  1.00 30.27      A    C
ATOM    118  CB  VAL A  23      62.534 148.228  54.437  1.00 28.40      A    C
ATOM    119  CG1 VAL A  23      62.467 148.293  52.897  1.00 26.74      A    C
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FIGURE 11-12

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ATOM    120  CG2 VAL A  23      62.530 149.611  55.028  1.00 27.24      A    C
ATOM    121  C   VAL A  23      61.164 146.188  54.135  1.00 31.67      A    C
ATOM    122  O   VAL A  23      60.322 146.140  53.242  1.00 32.85      A    O
ATOM    123  N   GLU A  24      61.958 145.172  54.425  1.00 31.69      A    N
ATOM    124  CA  GLU A  24      61.891 143.939  53.672  1.00 35.03      A    C
ATOM    125  CB  GLU A  24      63.101 143.067  54.006  1.00 33.12      A    C
ATOM    126  CG  GLU A  24      64.413 143.723  53.591  1.00 34.98      A    C
ATOM    127  CD  GLU A  24      65.632 143.124  54.285  1.00 38.12      A    C
ATOM    128  OE1 GLU A  24      65.466 142.252  55.172  1.00 39.09      A    O
ATOM    129  OE2 GLU A  24      66.759 143.531  53.942  1.00 39.16      A    O
ATOM    130  C   GLU A  24      60.594 143.189  53.920  1.00 36.61      A    C
ATOM    131  O   GLU A  24      60.020 142.623  52.993  1.00 35.81      A    O
ATOM    132  N   GLU A  25      60.115 143.201  55.161  1.00 38.85      A    N
ATOM    133  CA  GLU A  25      58.879 142.503  55.462  1.00 39.77      A    C
ATOM    134  CB  GLU A  25      58.683 142.338  56.969  1.00 41.27      A    C
ATOM    135  CG  GLU A  25      57.771 141.171  57.326  1.00 48.33      A    C
ATOM    136  CD  GLU A  25      58.436 139.796  57.127  1.00 55.92      A    C
ATOM    137  OE1 GLU A  25      59.178 139.598  56.125  1.00 59.88      A    O
ATOM    138  OE2 GLU A  25      58.205 138.901  57.978  1.00 58.51      A    O
ATOM    139  C   GLU A  25      57.695 143.254  54.862  1.00 38.94      A    C
ATOM    140  O   GLU A  25      56.737 142.641  54.392  1.00 40.83      A    O
ATOM    141  N   THR A  26      57.750 144.578  54.869  1.00 36.51      A    N
ATOM    142  CA  THR A  26      56.656 145.344  54.293  1.00 34.24      A    C
ATOM    143  CB  THR A  26      56.857 146.846  54.493  1.00 32.50      A    C
ATOM    144  OG1 THR A  26      56.777 147.148  55.886  1.00 32.26      A    O
ATOM    145  CG2 THR A  26      55.797 147.631  53.758  1.00 32.72      A    C
ATOM    146  C   THR A  26      56.553 145.030  52.801  1.00 35.06      A    C
ATOM    147  O   THR A  26      55.459 144.882  52.273  1.00 34.83      A    O
ATOM    148  N   ALA A  27      57.697 144.923  52.128  1.00 35.26      A    N
ATOM    149  CA  ALA A  27      57.708 144.603  50.705  1.00 36.62      A    C
ATOM    150  CB  ALA A  27      59.151 144.614  50.140  1.00 28.17      A    C
ATOM    151  C   ALA A  27      57.082 143.222  50.521  1.00 36.82      A    C
ATOM    152  O   ALA A  27      56.144 143.066  49.736  1.00 34.82      A    O
ATOM    153  N   ARG A  28      57.597 142.231  51.252  1.00 37.34      A    N
ATOM    154  CA  ARG A  28      57.075 140.868  51.159  1.00 38.66      A    C
ATOM    155  CB  ARG A  28      57.749 139.942  52.194  1.00 39.18      A    C
ATOM    156  CG  ARG A  28      59.213 139.598  51.885  1.00 43.03      A    C
ATOM    157  CD  ARG A  28      59.811 138.634  52.906  1.00 44.91      A    C
ATOM    158  NE  ARG A  28      61.266 138.504  52.770  1.00 52.87      A    N
ATOM    159  CZ  ARG A  28      61.891 138.030  51.688  1.00 54.87      A    C
ATOM    160  NH1 ARG A  28      61.197 137.629  50.622  1.00 54.99      A    N
ATOM    161  NH2 ARG A  28      63.217 137.957  51.666  1.00 52.87      A    N
ATOM    162  C   ARG A  28      55.550 140.796  51.323  1.00 38.29      A    C
ATOM    163  O   ARG A  28      54.869 140.144  50.534  1.00 36.09      A    O
ATOM    164  N   LEU A  29      55.016 141.463  52.341  1.00 38.77      A    N
ATOM    165  CA  LEU A  29      53.578 141.436  52.581  1.00 40.34      A    C
ATOM    166  CB  LEU A  29      53.248 142.115  53.917  1.00 40.41      A    C
ATOM    167  CG  LEU A  29      53.929 141.319  55.051  1.00 47.65      A    C
ATOM    168  CD1 LEU A  29      53.702 141.971  56.420  1.00 47.08      A    C
ATOM    169  CD2 LEU A  29      53.399 139.880  55.040  1.00 46.65      A    C
ATOM    170  C   LEU A  29      52.804 142.067  51.435  1.00 40.26      A    C
ATOM    171  O   LEU A  29      51.865 141.452  50.912  1.00 40.00      A    O
ATOM    172  N   ILE A  30      53.205 143.273  51.029  1.00 39.33      A    N
ATOM    173  CA  ILE A  30      52.543 143.959  49.921  1.00 38.33      A    C
ATOM    174  CB  ILE A  30      53.223 145.304  49.571  1.00 40.25      A    C
ATOM    175  CG2 ILE A  30      52.633 145.855  48.282  1.00 37.36      A    C
ATOM    176  CG1 ILE A  30      53.011 146.329  50.688  1.00 43.73      A    C
ATOM    177  CD1 ILE A  30      51.648 147.009  50.668  1.00 44.18      A    C
ATOM    178  C   ILE A  30      52.586 143.104  48.658  1.00 37.41      A    C
ATOM    179  O   ILE A  30      51.583 142.931  47.982  1.00 36.88      A    O
ATOM    180  N   PHE A  31      53.763 142.580  48.346  1.00 37.40      A    N
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FIGURE 11-13

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ATOM    181  CA  PHE A  31      53.963 141.777  47.151  1.00 39.36      A    C
ATOM    182  CB  PHE A  31      55.444 141.430  47.014  1.00 37.73      A    C
ATOM    183  CG  PHE A  31      56.291 142.597  46.647  1.00 35.28      A    C
ATOM    184  CD1 PHE A  31      57.660 142.578  46.868  1.00 35.82      A    C
ATOM    185  CD2 PHE A  31      55.722 143.721  46.074  1.00 37.21      A    C
ATOM    186  CE1 PHE A  31      58.445 143.654  46.528  1.00 30.09      A    C
ATOM    187  CE2 PHE A  31      56.505 144.810  45.730  1.00 36.64      A    C
ATOM    188  CZ  PHE A  31      57.872 144.772  45.961  1.00 34.06      A    C
ATOM    189  C   PHE A  31      53.122 140.516  47.110  1.00 41.49      A    C
ATOM    190  O   PHE A  31      52.589 140.157  46.059  1.00 41.51      A    O
ATOM    191  N   LYS A  32      53.013 139.841  48.249  1.00 42.27      A    N
ATOM    192  CA  LYS A  32      52.207 138.635  48.327  1.00 44.22      A    C
ATOM    193  CB  LYS A  32      52.355 137.987  49.710  1.00 47.19      A    C
ATOM    194  CG  LYS A  32      51.635 136.648  49.856  1.00 54.13      A    C
ATOM    195  CD  LYS A  32      51.912 135.982  51.211  1.00 57.81      A    C
ATOM    196  CE  LYS A  32      53.326 135.409  51.284  1.00 61.24      A    C
ATOM    197  NZ  LYS A  32      53.556 134.324  50.274  1.00 62.33      A    N
ATOM    198  C   LYS A  32      50.733 138.982  48.038  1.00 42.38      A    C
ATOM    199  O   LYS A  32      50.070 138.280  47.281  1.00 42.93      A    O
ATOM    200  N   ASP A  33      50.227 140.066  48.620  1.00 40.40      A    N
ATOM    201  CA  ASP A  33      48.841 140.467  48.384  1.00 41.81      A    C
ATOM    202  CB  ASP A  33      48.458 141.670  49.263  1.00 43.40      A    C
ATOM    203  CG  ASP A  33      48.322 141.311  50.741  1.00 48.05      A    C
ATOM    204  OD1 ASP A  33      48.402 140.111  51.080  1.00 48.73      A    O
ATOM    205  OD2 ASP A  33      48.128 142.236  51.568  1.00 51.80      A    O
ATOM    206  C   ASP A  33      48.568 140.818  46.907  1.00 42.21      A    C
ATOM    207  O   ASP A  33      47.424 140.748  46.449  1.00 43.53      A    O
ATOM    208  N   TYR A  34      49.612 141.218  46.184  1.00 40.10      A    N
ATOM    209  CA  TYR A  34      49.508 141.568  44.769  1.00 39.26      A    C
ATOM    210  CB  TYR A  34      50.390 142.779  44.450  1.00 36.04      A    C
ATOM    211  CG  TYR A  34      49.755 144.119  44.736  1.00 34.38      A    C
ATOM    212  CD1 TYR A  34      49.147 144.854  43.719  1.00 32.49      A    C
ATOM    213  CE1 TYR A  34      48.566 146.091  43.974  1.00 31.36      A    C
ATOM    214  CD2 TYR A  34      49.762 144.657  46.024  1.00 35.61      A    C
ATOM    215  CE2 TYR A  34      49.176 145.894  46.291  1.00 34.99      A    C
ATOM    216  CZ  TYR A  34      48.580 146.604  45.262  1.00 33.61      A    C
ATOM    217  OH  TYR A  34      47.972 147.814  45.528  1.00 35.65      A    O
ATOM    218  C   TYR A  34      49.944 140.385  43.903  1.00 38.44      A    C
ATOM    219  O   TYR A  34      50.134 140.511  42.694  1.00 42.38      A    O
ATOM    220  N   GLN A  35      50.109 139.239  44.537  1.00 37.36      A    N
ATOM    221  CA  GLN A  35      50.506 138.016  43.858  1.00 39.07      A    C
ATOM    222  CB  GLN A  35      49.407 137.567  42.886  1.00 39.20      A    C
ATOM    223  CG  GLN A  35      48.093 137.259  43.582  1.00 42.54      A    C
ATOM    224  CD  GLN A  35      48.253 136.218  44.676  1.00 44.20      A    C
ATOM    225  OE1 GLN A  35      48.510 135.050  44.399  1.00 46.52      A    O
ATOM    226  NE2 GLN A  35      48.116 136.643  45.928  1.00 47.31      A    N
ATOM    227  C   GLN A  35      51.845 138.044  43.137  1.00 38.69      A    C
ATOM    228  O   GLN A  35      52.015 137.370  42.125  1.00 40.50      A    O
ATOM    229  N   TYR A  36      52.796 138.811  43.650  1.00 38.35      A    N
ATOM    230  CA  TYR A  36      54.125 138.854  43.054  1.00 36.94      A    C
ATOM    231  CB  TYR A  36      54.692 140.260  43.119  1.00 34.85      A    C
ATOM    232  CG  TYR A  36      54.134 141.156  42.053  1.00 34.00      A    C
ATOM    233  CD1 TYR A  36      54.886 141.477  40.915  1.00 30.17      A    C
ATOM    234  CE1 TYR A  36      54.344 142.276  39.902  1.00 30.91      A    C
ATOM    235  CD2 TYR A  36      52.838 141.653  42.153  1.00 33.30      A    C
ATOM    236  CE2 TYR A  36      52.292 142.439  41.153  1.00 32.98      A    C
ATOM    237  CZ  TYR A  36      53.045 142.743  40.030  1.00 32.10      A    C
ATOM    238  OH  TYR A  36      52.465 143.472  39.019  1.00 35.58      A    O
ATOM    239  C   TYR A  36      54.983 137.906  43.855  1.00 37.81      A    C
ATOM    240  O   TYR A  36      55.028 137.999  45.072  1.00 41.95      A    O
ATOM    241  N   GLN A  37      55.655 136.979  43.187  1.00 39.64      A    N
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FIGURE 11-14

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ATOM    242  CA  GLN A  37      56.477 136.016  43.901  1.00 40.67      A    C
ATOM    243  CB  GLN A  37      56.062 134.598  43.511  1.00 43.20      A    C
ATOM    244  CG  GLN A  37      54.736 134.164  44.147  1.00 48.28      A    C
ATOM    245  CD  GLN A  37      54.202 132.866  43.567  1.00 52.76      A    C
ATOM    246  OE1 GLN A  37      53.603 132.856  42.489  1.00 54.77      A    O
ATOM    247  NE2 GLN A  37      54.428 131.758  44.274  1.00 54.90      A    N
ATOM    248  C   GLN A  37      57.982 136.213  43.727  1.00 42.42      A    C
ATOM    249  O   GLN A  37      58.485 136.543  42.642  1.00 40.29      A    O
ATOM    250  N   GLU A  38      58.697 136.008  44.825  1.00 42.52      A    N
ATOM    251  CA  GLU A  38      60.132 136.188  44.831  1.00 42.23      A    C
ATOM    252  CB  GLU A  38      60.680 136.153  46.260  1.00 39.16      A    C
ATOM    253  CG  GLU A  38      62.191 136.106  46.288  1.00 41.31      A    C
ATOM    254  CD  GLU A  38      62.779 136.372  47.653  1.00 43.49      A    C
ATOM    255  OE1 GLU A  38      62.124 136.044  48.667  1.00 44.17      A    O
ATOM    256  OE2 GLU A  38      63.910 136.899  47.708  1.00 42.64      A    O
ATOM    257  C   GLU A  38      60.912 135.213  43.982  1.00 41.22      A    C
ATOM    258  O   GLU A  38      60.619 134.029  43.907  1.00 41.31      A    O
ATOM    259  N   ILE A  39      61.933 135.747  43.344  1.00 41.99      A    N
ATOM    260  CA  ILE A  39      62.812 134.962  42.514  1.00 42.63      A    C
ATOM    261  CB  ILE A  39      62.615 135.327  41.054  1.00 43.23      A    C
ATOM    262  CG2 ILE A  39      62.711 136.833  40.896  1.00 44.67      A    C
ATOM    263  CG1 ILE A  39      63.634 134.604  40.188  1.00 42.00      A    C
ATOM    264  CD1 ILE A  39      63.228 134.608  38.752  1.00 47.96      A    C
ATOM    265  C   ILE A  39      64.195 135.378  42.978  1.00 42.75      A    C
ATOM    266  O   ILE A  39      64.452 136.572  43.175  1.00 43.83      A    O
ATOM    267  N   ARG A  40      65.074 134.411  43.196  1.00 40.69      A    N
ATOM    268  CA  ARG A  40      66.413 134.751  43.648  1.00 41.05      A    C
ATOM    269  CB  ARG A  40      66.684 134.187  45.041  1.00 38.81      A    C
ATOM    270  CG  ARG A  40      65.719 134.689  46.080  1.00 41.05      A    C
ATOM    271  CD  ARG A  40      66.143 134.230  47.450  1.00 40.05      A    C
ATOM    272  NE  ARG A  40      65.109 134.515  48.434  1.00 39.33      A    N
ATOM    273  CZ  ARG A  40      65.182 134.162  49.712  1.00 38.94      A    C
ATOM    274  NH1 ARG A  40      66.248 133.511  50.166  1.00 33.51      A    N
ATOM    275  NH2 ARG A  40      64.182 134.452  50.535  1.00 39.56      A    N
ATOM    276  C   ARG A  40      67.479 134.268  42.692  1.00 40.17      A    C
ATOM    277  O   ARG A  40      67.622 133.074  42.445  1.00 39.69      A    O
ATOM    278  N   THR A  41      68.229 135.233  42.190  1.00 39.95      A    N
ATOM    279  CA  THR A  41      69.315 135.036  41.253  1.00 41.63      A    C
ATOM    280  CB  THR A  41      69.323 136.203  40.274  1.00 40.52      A    C
ATOM    281  OG1 THR A  41      68.392 135.913  39.225  1.00 43.65      A    O
ATOM    282  CG2 THR A  41      70.714 136.464  39.716  1.00 46.00      A    C
ATOM    283  C   THR A  41      70.650 134.946  41.985  1.00 42.73      A    C
ATOM    284  O   THR A  41      70.802 135.470  43.085  1.00 43.15      A    O
ATOM    285  N   PRO A  42      71.641 134.275  41.381  1.00 43.47      A    N
ATOM    286  CD  PRO A  42      71.616 133.478  40.145  1.00 44.24      A    C
ATOM    287  CA  PRO A  42      72.940 134.160  42.042  1.00 43.71      A    C
ATOM    288  CB  PRO A  42      73.720 133.242  41.105  1.00 44.91      A    C
ATOM    289  CG  PRO A  42      72.649 132.430  40.446  1.00 45.17      A    C
ATOM    290  C   PRO A  42      73.596 135.527  42.181  1.00 42.81      A    C
ATOM    291  O   PRO A  42      73.252 136.456  41.452  1.00 39.97      A    O
ATOM    292  N   ILE A  43      74.528 135.643  43.125  1.00 44.34      A    N
ATOM    293  CA  ILE A  43      75.248 136.893  43.350  1.00 45.56      A    C
ATOM    294  CB  ILE A  43      76.223 136.779  44.543  1.00 44.47      A    C
ATOM    295  CG2 ILE A  43      77.221 137.928  44.506  1.00 40.71      A    C
ATOM    296  CG1 ILE A  43      75.441 136.732  45.865  1.00 43.28      A    C
ATOM    297  CD1 ILE A  43      74.641 137.987  46.168  1.00 42.18      A    C
ATOM    298  C   ILE A  43      76.051 137.224  42.097  1.00 48.35      A    C
ATOM    299  O   ILE A  43      76.280 138.393  41.780  1.00 50.03      A    O
ATOM    300  N   PHE A  44      76.488 136.189  41.391  1.00 50.81      A    N
ATOM    301  CA  PHE A  44      77.245 136.405  40.172  1.00 55.25      A    C
ATOM    302  CB  PHE A  44      78.710 136.006  40.355  1.00 57.11      A    C
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FIGURE 11-15

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ATOM    303  CG  PHE A  44      78.905 134.606  40.831  1.00 60.47      A    C
ATOM    304  CD1 PHE A  44      78.904 134.316  42.188  1.00 61.19      A    C
ATOM    305  CD2 PHE A  44      79.109 133.571  39.918  1.00 62.92      A    C
ATOM    306  CE1 PHE A  44      79.106 133.009  42.638  1.00 64.67      A    C
ATOM    307  CE2 PHE A  44      79.314 132.254  40.353  1.00 64.03      A    C
ATOM    308  CZ  PHE A  44      79.314 131.972  41.718  1.00 64.63      A    C
ATOM    309  C   PHE A  44      76.650 135.664  38.983  1.00 55.67      A    C
ATOM    310  O   PHE A  44      76.042 134.607  39.138  1.00 56.11      A    O
ATOM    311  N   GLU A  45      76.823 136.251  37.804  1.00 55.67      A    N
ATOM    312  CA  GLU A  45      76.327 135.692  36.553  1.00 57.75      A    C
ATOM    313  CB  GLU A  45      75.301 136.637  35.925  1.00 57.92      A    C
ATOM    314  CG  GLU A  45      74.015 136.813  36.700  1.00 57.03      A    C
ATOM    315  CD  GLU A  45      72.916 135.916  36.191  1.00 57.02      A    C
ATOM    316  OE1 GLU A  45      72.695 135.892  34.964  1.00 58.64      A    O
ATOM    317  OE2 GLU A  45      72.265 135.245  37.013  1.00 58.63      A    O
ATOM    318  C   GLU A  45      77.502 135.551  35.591  1.00 59.28      A    C
ATOM    319  O   GLU A  45      78.580 136.100  35.827  1.00 59.12      A    O
ATOM    320  N   HIS A  46      77.303 134.819  34.504  1.00 60.92      A    N
ATOM    321  CA  HIS A  46      78.375 134.686  33.538  1.00 63.15      A    C
ATOM    322  CB  HIS A  46      78.104 133.523  32.591  1.00 64.78      A    C
ATOM    323  CG  HIS A  46      78.633 132.218  33.095  1.00 68.09      A    C
ATOM    324  CD2 HIS A  46      77.999 131.124  33.580  1.00 69.37      A    C
ATOM    325  ND1 HIS A  46      79.983 131.959  33.206  1.00 70.13      A    N
ATOM    326  CE1 HIS A  46      80.159 130.764  33.741  1.00 70.50      A    C
ATOM    327  NE2 HIS A  46      78.971 130.236  33.979  1.00 72.35      A    N
ATOM    328  C   HIS A  46      78.448 136.007  32.795  1.00 64.28      A    C
ATOM    329  O   HIS A  46      77.429 136.538  32.360  1.00 64.88      A    O
ATOM    330  N   TYR A  47      79.661 136.539  32.682  1.00 65.53      A    N
ATOM    331  CA  TYR A  47      79.923 137.823  32.034  1.00 66.93      A    C
ATOM    332  CB  TYR A  47      81.375 137.884  31.571  1.00 67.66      A    C
ATOM    333  CG  TYR A  47      81.789 139.265  31.121  1.00 69.36      A    C
ATOM    334  CD1 TYR A  47      82.103 140.255  32.055  1.00 69.90      A    C
ATOM    335  CE1 TYR A  47      82.456 141.546  31.652  1.00 71.18      A    C
ATOM    336  CD2 TYR A  47      81.840 139.596  29.765  1.00 69.70      A    C
ATOM    337  CE2 TYR A  47      82.192 140.889  29.349  1.00 71.20      A    C
ATOM    338  CZ  TYR A  47      82.497 141.857  30.300  1.00 71.39      A    C
ATOM    339  OH  TYR A  47      82.832 143.134  29.908  1.00 72.13      A    O
ATOM    340  C   TYR A  47      79.037 138.228  30.857  1.00 67.15      A    C
ATOM    341  O   TYR A  47      78.430 139.298  30.872  1.00 65.71      A    O
ATOM    342  N   GLU A  48      78.984 137.381  29.833  1.00 69.31      A    N
ATOM    343  CA  GLU A  48      78.205 137.672  28.632  1.00 71.99      A    C
ATOM    344  CB  GLU A  48      78.323 136.509  27.641  1.00 73.56      A    C
ATOM    345  CG  GLU A  48      79.744 136.338  27.086  1.00 78.25      A    C
ATOM    346  CD  GLU A  48      79.818 135.393  25.887  1.00 81.71      A    C
ATOM    347  OE1 GLU A  48      80.930 135.211  25.335  1.00 81.76      A    O
ATOM    348  OE2 GLU A  48      78.768 134.835  25.493  1.00 83.17      A    O
ATOM    349  C   GLU A  48      76.737 138.035  28.866  1.00 72.01      A    C
ATOM    350  O   GLU A  48      76.197 138.905  28.182  1.00 71.81      A    O
ATOM    351  N   VAL A  49      76.095 137.379  29.827  1.00 72.25      A    N
ATOM    352  CA  VAL A  49      74.696 137.662  30.144  1.00 72.29      A    C
ATOM    353  CB  VAL A  49      74.184 136.753  31.293  1.00 72.64      A    C
ATOM    354  CG1 VAL A  49      72.846 137.268  31.815  1.00 73.26      A    C
ATOM    355  CG2 VAL A  49      74.043 135.321  30.802  1.00 72.42      A    C
ATOM    356  C   VAL A  49      74.528 139.118  30.575  1.00 71.91      A    C
ATOM    357  O   VAL A  49      73.630 139.821  30.113  1.00 72.94      A    O
ATOM    358  N   ILE A  50      75.404 139.567  31.464  1.00 71.27      A    N
ATOM    359  CA  ILE A  50      75.346 140.930  31.968  1.00 70.05      A    C
ATOM    360  CB  ILE A  50      76.160 141.050  33.268  1.00 68.01      A    C
ATOM    361  CG2 ILE A  50      76.094 142.469  33.803  1.00 67.22      A    C
ATOM    362  CG1 ILE A  50      75.616 140.053  34.292  1.00 67.41      A    C
ATOM    363  CD1 ILE A  50      74.105 140.132  34.487  1.00 65.65      A    C
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FIGURE 11-16

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ATOM    364  C   ILE A  50      75.808 141.992  30.966  1.00 70.69      A    C
ATOM    365  O   ILE A  50      75.226 143.077  30.901  1.00 70.32      A    O
ATOM    366  N   SER A  51      76.848 141.691  30.191  1.00 70.94      A    N
ATOM    367  CA  SER A  51      77.331 142.652  29.205  1.00 71.62      A    C
ATOM    368  CB  SER A  51      78.672 142.202  28.600  1.00 72.28      A    C
ATOM    369  OG  SER A  51      78.531 141.034  27.810  1.00 72.75      A    O
ATOM    370  C   SER A  51      76.287 142.817  28.107  1.00 71.03      A    C
ATOM    371  O   SER A  51      76.063 143.915  27.608  1.00 71.22      A    O
ATOM    372  N   ARG A  52      75.637 141.719  27.748  1.00 72.03      A    N
ATOM    373  CA  ARG A  52      74.611 141.745  26.716  1.00 74.35      A    C
ATOM    374  CB  ARG A  52      74.123 140.315  26.433  1.00 76.53      A    C
ATOM    375  CG  ARG A  52      73.052 140.181  25.348  1.00 79.09      A    C
ATOM    376  CD  ARG A  52      73.587 140.533  23.961  1.00 82.08      A    C
ATOM    377  NE  ARG A  52      72.655 140.160  22.894  1.00 84.03      A    N
ATOM    378  CZ  ARG A  52      72.312 138.907  22.594  1.00 84.49      A    C
ATOM    379  NH1 ARG A  52      72.822 137.887  23.277  1.00 84.08      A    N
ATOM    380  NH2 ARG A  52      71.456 138.671  21.608  1.00 83.77      A    N
ATOM    381  C   ARG A  52      73.436 142.620  27.154  1.00 74.48      A    C
ATOM    382  O   ARG A  52      73.031 143.532  26.436  1.00 74.33      A    O
ATOM    383  N   SER A  53      72.913 142.349  28.348  1.00 75.57      A    N
ATOM    384  CA  SER A  53      71.765 143.079  28.886  1.00 76.79      A    C
ATOM    385  CB  SER A  53      71.071 142.237  29.956  1.00 76.20      A    C
ATOM    386  OG  SER A  53      70.009 142.969  30.543  1.00 75.30      A    O
ATOM    387  C   SER A  53      72.023 144.470  29.461  1.00 77.50      A    C
ATOM    388  O   SER A  53      71.367 145.439  29.073  1.00 77.54      A    O
ATOM    389  N   VAL A  54      72.960 144.565  30.397  1.00 78.44      A    N
ATOM    390  CA  VAL A  54      73.272 145.843  31.027  1.00 79.41      A    C
ATOM    391  CB  VAL A  54      73.638 145.639  32.519  1.00 79.37      A    C
ATOM    392  CG1 VAL A  54      73.733 146.985  33.228  1.00 78.49      A    C
ATOM    393  CG2 VAL A  54      72.598 144.748  33.188  1.00 77.95      A    C
ATOM    394  C   VAL A  54      74.412 146.574  30.314  1.00 80.80      A    C
ATOM    395  O   VAL A  54      74.371 147.797  30.162  1.00 81.00      A    O
ATOM    396  N   GLY A  55      75.424 145.824  29.878  1.00 82.17      A    N
ATOM    397  CA  GLY A  55      76.552 146.422  29.178  1.00 83.96      A    C
ATOM    398  C   GLY A  55      77.905 146.175  29.827  1.00 85.32      A    C
ATOM    399  O   GLY A  55      78.334 145.033  29.991  1.00 85.15      A    O
ATOM    400  N   ASP A  56      78.589 147.259  30.178  1.00 86.70      A    N
ATOM    401  CA  ASP A  56      79.895 147.185  30.830  1.00 87.94      A    C
ATOM    402  CB  ASP A  56      80.977 146.728  29.838  1.00 88.64      A    C
ATOM    403  CG  ASP A  56      80.794 147.317  28.451  1.00 89.62      A    C
ATOM    404  OD1 ASP A  56      80.950 148.547  28.288  1.00 90.29      A    O
ATOM    405  OD2 ASP A  56      80.491 146.539  27.520  1.00 89.88      A    O
ATOM    406  C   ASP A  56      80.242 148.545  31.419  1.00 88.11      A    C
ATOM    407  O   ASP A  56      80.252 148.718  32.639  1.00 88.64      A    O
ATOM    408  N   THR A  57      80.522 149.507  30.548  1.00 87.83      A    N
ATOM    409  CA  THR A  57      80.840 150.861  30.978  1.00 87.54      A    C
ATOM    410  CB  THR A  57      79.542 151.608  31.336  1.00 88.11      A    C
ATOM    411  OG1 THR A  57      78.759 150.801  32.227  1.00 87.46      A    O
ATOM    412  CG2 THR A  57      78.729 151.896  30.074  1.00 87.40      A    C
ATOM    413  C   THR A  57      81.824 150.949  32.155  1.00 86.68      A    C
ATOM    414  O   THR A  57      82.071 152.039  32.678  1.00 86.82      A    O
ATOM    415  N   THR A  58      82.376 149.803  32.556  1.00 84.82      A    N
ATOM    416  CA  THR A  58      83.353 149.701  33.646  1.00 83.71      A    C
ATOM    417  CB  THR A  58      84.457 150.786  33.520  1.00 84.68      A    C
ATOM    418  OG1 THR A  58      85.036 150.726  32.210  1.00 86.04      A    O
ATOM    419  CG2 THR A  58      85.562 150.563  34.555  1.00 84.16      A    C
ATOM    420  C   THR A  58      82.793 149.750  35.070  1.00 81.92      A    C
ATOM    421  O   THR A  58      83.497 149.406  36.020  1.00 81.48      A    O
ATOM    422  N   ASP A  59      81.544 150.175  35.237  1.00 79.50      A    N
ATOM    423  CA  ASP A  59      80.976 150.224  36.580  1.00 76.99      A    C
ATOM    424  CB  ASP A  59      79.771 151.177  36.625  1.00 77.44      A    C
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FIGURE 11-17

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ATOM    425  CG  ASP A  59      78.476 150.523  36.162  1.00 78.40      A    C
ATOM    426  OD1 ASP A  59      78.410 150.047  35.005  1.00 78.78      A    O
ATOM    427  OD2 ASP A  59      77.518 150.491  36.963  1.00 77.39      A    O
ATOM    428  C   ASP A  59      80.568 148.809  37.019  1.00 75.26      A    C
ATOM    429  O   ASP A  59      80.183 148.581  38.168  1.00 74.65      A    O
ATOM    430  N   ILE A  60      80.686 147.858  36.099  1.00 72.34      A    N
ATOM    431  CA  ILE A  60      80.326 146.471  36.362  1.00 71.06      A    C
ATOM    432  CB  ILE A  60      79.751 145.832  35.094  1.00 70.42      A    C
ATOM    433  CG2 ILE A  60      79.570 144.344  35.289  1.00 68.18      A    C
ATOM    434  CG1 ILE A  60      78.433 146.521  34.745  1.00 71.01      A    C
ATOM    435  CD1 ILE A  60      77.867 146.125  33.411  1.00 71.90      A    C
ATOM    436  C   ILE A  60      81.498 145.630  36.858  1.00 70.98      A    C
ATOM    437  O   ILE A  60      82.552 145.580  36.221  1.00 71.35      A    O
ATOM    438  N   VAL A  61      81.304 144.959  37.991  1.00 69.70      A    N
ATOM    439  CA  VAL A  61      82.349 144.126  38.574  1.00 68.53      A    C
ATOM    440  CB  VAL A  61      82.144 143.951  40.090  1.00 67.41      A    C
ATOM    441  CG1 VAL A  61      83.258 143.106  40.673  1.00 65.73      A    C
ATOM    442  CG2 VAL A  61      82.099 145.313  40.764  1.00 67.41      A    C
ATOM    443  C   VAL A  61      82.413 142.749  37.933  1.00 69.09      A    C
ATOM    444  O   VAL A  61      81.494 141.944  38.057  1.00 69.31      A    O
ATOM    445  N   SER A  62      83.516 142.490  37.244  1.00 71.12      A    N
ATOM    446  CA  SER A  62      83.732 141.218  36.578  1.00 72.08      A    C
ATOM    447  CB  SER A  62      83.586 141.390  35.071  1.00 71.44      A    C
ATOM    448  OG  SER A  62      82.314 141.923  34.758  1.00 70.64      A    O
ATOM    449  C   SER A  62      85.127 140.705  36.913  1.00 74.11      A    C
ATOM    450  O   SER A  62      86.009 141.476  37.301  1.00 74.47      A    O
ATOM    451  N   LYS A  63      85.324 139.403  36.759  1.00 75.47      A    N
ATOM    452  CA  LYS A  63      86.609 138.797  37.063  1.00 77.45      A    C
ATOM    453  CB  LYS A  63      86.861 138.841  38.570  1.00 77.68      A    C
ATOM    454  CG  LYS A  63      85.779 138.153  39.392  1.00 78.23      A    C
ATOM    455  CD  LYS A  63      86.096 138.202  40.877  1.00 79.79      A    C
ATOM    456  CE  LYS A  63      85.016 137.526  41.706  1.00 79.00      A    C
ATOM    457  NZ  LYS A  63      85.336 137.576  43.158  1.00 78.88      A    N
ATOM    458  C   LYS A  63      86.659 137.353  36.593  1.00 79.07      A    C
ATOM    459  O   LYS A  63      85.626 136.734  36.333  1.00 79.40      A    O
ATOM    460  N   GLU A  64      87.875 136.826  36.485  1.00 81.05      A    N
ATOM    461  CA  GLU A  64      88.091 135.448  36.066  1.00 81.88      A    C
ATOM    462  CB  GLU A  64      89.430 135.327  35.329  1.00 83.62      A    C
ATOM    463  CG  GLU A  64      89.543 136.208  34.077  1.00 85.98      A    C
ATOM    464  CD  GLU A  64      89.155 135.483  32.793  1.00 87.50      A    C
ATOM    465  OE1 GLU A  64      89.969 134.666  32.305  1.00 88.62      A    O
ATOM    466  OE2 GLU A  64      88.042 135.724  32.272  1.00 86.64      A    O
ATOM    467  C   GLU A  64      88.096 134.597  37.333  1.00 81.92      A    C
ATOM    468  O   GLU A  64      88.973 134.727  38.188  1.00 81.83      A    O
ATOM    469  N   MET A  65      87.096 133.740  37.460  1.00 81.47      A    N
ATOM    470  CA  MET A  65      86.984 132.881  38.623  1.00 81.53      A    C
ATOM    471  CB  MET A  65      85.522 132.809  39.051  1.00 82.79      A    C
ATOM    472  CG  MET A  65      85.264 132.115  40.365  1.00 84.19      A    C
ATOM    473  SD  MET A  65      83.486 132.037  40.658  1.00 86.63      A    S
ATOM    474  CE  MET A  65      83.149 133.750  41.180  1.00 86.12      A    C
ATOM    475  C   MET A  65      87.499 131.498  38.246  1.00 81.23      A    C
ATOM    476  O   MET A  65      87.007 130.888  37.295  1.00 80.85      A    O
ATOM    477  N   TYR A  66      88.496 131.010  38.980  1.00 81.00      A    N
ATOM    478  CA  TYR A  66      89.062 129.697  38.697  1.00 80.12      A    C
ATOM    479  CB  TYR A  66      90.277 129.414  39.581  1.00 82.28      A    C
ATOM    480  CG  TYR A  66      90.733 127.973  39.485  1.00 85.42      A    C
ATOM    481  CD1 TYR A  66      91.262 127.464  38.296  1.00 86.29      A    C
ATOM    482  CE1 TYR A  66      91.625 126.121  38.185  1.00 87.19      A    C
ATOM    483  CD2 TYR A  66      90.582 127.100  40.566  1.00 86.31      A    C
ATOM    484  CE2 TYR A  66      90.941 125.756  40.466  1.00 86.59      A    C
ATOM    485  CZ  TYR A  66      91.460 125.273  39.274  1.00 87.37      A    C
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FIGURE 11-18

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ATOM    486  OH  TYR A  66      91.798 123.941  39.167  1.00 87.73      A    O
ATOM    487  C   TYR A  66      88.043 128.588  38.901  1.00 78.34      A    C
ATOM    488  O   TYR A  66      87.365 128.533  39.927  1.00 78.10      A    O
ATOM    489  N   ASP A  67      87.953 127.702  37.914  1.00 76.25      A    N
ATOM    490  CA  ASP A  67      87.028 126.581  37.954  1.00 75.15      A    C
ATOM    491  CB  ASP A  67      85.798 126.880  37.095  1.00 74.06      A    C
ATOM    492  CG  ASP A  67      84.664 125.905  37.337  1.00 74.41      A    C
ATOM    493  OD1 ASP A  67      84.004 126.008  38.395  1.00 75.25      A    O
ATOM    494  OD2 ASP A  67      84.434 125.032  36.473  1.00 71.90      A    O
ATOM    495  C   ASP A  67      87.758 125.360  37.405  1.00 75.27      A    C
ATOM    496  O   ASP A  67      88.458 125.444  36.399  1.00 75.91      A    O
ATOM    497  N   PHE A  68      87.594 124.227  38.073  1.00 74.99      A    N
ATOM    498  CA  PHE A  68      88.244 122.991  37.664  1.00 74.81      A    C
ATOM    499  CB  PHE A  68      88.240 122.001  38.833  1.00 74.69      A    C
ATOM    500  CG  PHE A  68      89.002 120.737  38.565  1.00 75.31      A    C
ATOM    501  CD1 PHE A  68      90.379 120.767  38.363  1.00 76.17      A    C
ATOM    502  CD2 PHE A  68      88.347 119.512  38.523  1.00 74.46      A    C
ATOM    503  CE1 PHE A  68      91.094 119.590  38.122  1.00 75.49      A    C
ATOM    504  CE2 PHE A  68      89.051 118.334  38.282  1.00 75.42      A    C
ATOM    505  CZ  PHE A  68      90.428 118.373  38.082  1.00 74.43      A    C
ATOM    506  C   PHE A  68      87.541 122.363  36.464  1.00 74.73      A    C
ATOM    507  O   PHE A  68      88.153 122.117  35.426  1.00 75.22      A    O
ATOM    508  N   TYR A  69      86.246 122.120  36.619  1.00 73.94      A    N
ATOM    509  CA  TYR A  69      85.425 121.492  35.590  1.00 73.78      A    C
ATOM    510  CB  TYR A  69      84.026 121.307  36.154  1.00 70.56      A    C
ATOM    511  CG  TYR A  69      84.109 120.760  37.554  1.00 69.36      A    C
ATOM    512  CD1 TYR A  69      84.763 119.554  37.803  1.00 67.27      A    C
ATOM    513  CE1 TYR A  69      84.919 119.075  39.090  1.00 65.87      A    C
ATOM    514  CD2 TYR A  69      83.606 121.475  38.640  1.00 68.09      A    C
ATOM    515  CE2 TYR A  69      83.757 121.002  39.936  1.00 66.02      A    C
ATOM    516  CZ  TYR A  69      84.416 119.802  40.151  1.00 65.61      A    C
ATOM    517  OH  TYR A  69      84.573 119.319  41.423  1.00 62.44      A    O
ATOM    518  C   TYR A  69      85.390 122.225  34.261  1.00 75.51      A    C
ATOM    519  O   TYR A  69      85.093 121.635  33.224  1.00 75.60      A    O
ATOM    520  N   ASP A  70      85.691 123.514  34.297  1.00 78.33      A    N
ATOM    521  CA  ASP A  70      85.730 124.319  33.088  1.00 81.49      A    C
ATOM    522  CB  ASP A  70      84.571 125.323  33.078  1.00 82.64      A    C
ATOM    523  CG  ASP A  70      83.224 124.656  32.798  1.00 84.49      A    C
ATOM    524  OD1 ASP A  70      83.087 124.010  31.735  1.00 84.97      A    O
ATOM    525  OD2 ASP A  70      82.301 124.775  33.634  1.00 84.80      A    O
ATOM    526  C   ASP A  70      87.085 125.021  33.088  1.00 83.11      A    C
ATOM    527  O   ASP A  70      88.113 124.377  32.861  1.00 82.77      A    O
ATOM    528  N   LYS A  71      87.092 126.326  33.351  1.00 85.12      A    N
ATOM    529  CA  LYS A  71      88.334 127.100  33.405  1.00 86.75      A    C
ATOM    530  CB  LYS A  71      89.261 126.741  32.235  1.00 87.79      A    C
ATOM    531  CG  LYS A  71      90.678 127.278  32.403  1.00 88.42      A    C
ATOM    532  CD  LYS A  71      91.267 126.839  33.741  1.00 88.05      A    C
ATOM    533  CE  LYS A  71      92.597 127.520  34.016  1.00 88.28      A    C
ATOM    534  NZ  LYS A  71      93.078 127.238  35.396  1.00 87.56      A    N
ATOM    535  C   LYS A  71      88.081 128.603  33.397  1.00 86.77      A    C
ATOM    536  O   LYS A  71      88.925 129.382  33.840  1.00 87.22      A    O
ATOM    537  N   ARG A  74      85.729 130.235  33.954  1.00 67.25      A    N
ATOM    538  CA  ARG A  74      84.532 130.979  34.328  1.00 67.04      A    C
ATOM    539  CB  ARG A  74      83.910 130.378  35.597  1.00 67.30      A    C
ATOM    540  CG  ARG A  74      83.464 128.918  35.444  1.00 70.47      A    C
ATOM    541  CD  ARG A  74      81.961 128.716  35.677  1.00 72.04      A    C
ATOM    542  NE  ARG A  74      81.621 128.339  37.053  1.00 73.27      A    N
ATOM    543  CZ  ARG A  74      81.804 129.110  38.124  1.00 73.04      A    C
ATOM    544  NH1 ARG A  74      81.461 128.672  39.328  1.00 72.05      A    N
ATOM    545  NH2 ARG A  74      82.327 130.320  37.998  1.00 73.36      A    N
ATOM    546  C   ARG A  74      84.820 132.473  34.534  1.00 66.08      A    C
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FIGURE 11-19

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ATOM    547  O   ARG A  74      85.462 132.877  35.506  1.00 65.99      A    O
ATOM    548  N   HIS A  75      84.347 133.282  33.594  1.00 64.57      A    N
ATOM    549  CA  HIS A  75      84.510 134.732  33.640  1.00 64.04      A    C
ATOM    550  CB  HIS A  75      84.831 135.238  32.229  1.00 65.94      A    C
ATOM    551  CG  HIS A  75      85.016 136.718  32.139  1.00 68.26      A    C
ATOM    552  CD2 HIS A  75      84.592 137.613  31.216  1.00 69.45      A    C
ATOM    553  ND1 HIS A  75      85.740 137.438  33.066  1.00 70.20      A    N
ATOM    554  CE1 HIS A  75      85.751 138.713  32.719  1.00 70.75      A    C
ATOM    555  NE2 HIS A  75      85.061 138.846  31.600  1.00 69.81      A    N
ATOM    556  C   HIS A  75      83.170 135.291  34.145  1.00 62.57      A    C
ATOM    557  O   HIS A  75      82.246 135.521  33.363  1.00 62.59      A    O
ATOM    558  N   VAL A  76      83.075 135.507  35.455  1.00 60.38      A    N
ATOM    559  CA  VAL A  76      81.834 135.972  36.068  1.00 59.11      A    C
ATOM    560  CB  VAL A  76      81.571 135.224  37.390  1.00 58.98      A    C
ATOM    561  CG1 VAL A  76      81.554 133.729  37.145  1.00 60.37      A    C
ATOM    562  CG2 VAL A  76      82.634 135.581  38.405  1.00 60.49      A    C
ATOM    563  C   VAL A  76      81.677 137.462  36.349  1.00 57.65      A    C
ATOM    564  O   VAL A  76      82.614 138.247  36.238  1.00 58.57      A    O
ATOM    565  N   THR A  77      80.463 137.828  36.738  1.00 55.09      A    N
ATOM    566  CA  THR A  77      80.125 139.204  37.044  1.00 52.21      A    C
ATOM    567  CB  THR A  77      79.439 139.886  35.840  1.00 53.39      A    C
ATOM    568  OG1 THR A  77      80.309 139.850  34.703  1.00 55.37      A    O
ATOM    569  CG2 THR A  77      79.093 141.329  36.174  1.00 52.20      A    C
ATOM    570  C   THR A  77      79.153 139.254  38.214  1.00 49.50      A    C
ATOM    571  O   THR A  77      78.142 138.542  38.224  1.00 46.95      A    O
ATOM    572  N   LEU A  78      79.464 140.090  39.201  1.00 47.07      A    N
ATOM    573  CA  LEU A  78      78.585 140.258  40.358  1.00 44.51      A    C
ATOM    574  CB  LEU A  78      79.273 141.122  41.411  1.00 44.51      A    C
ATOM    575  CG  LEU A  78      80.587 140.531  41.930  1.00 45.20      A    C
ATOM    576  CD1 LEU A  78      81.274 141.530  42.836  1.00 43.61      A    C
ATOM    577  CD2 LEU A  78      80.310 139.230  42.660  1.00 44.61      A    C
ATOM    578  C   LEU A  78      77.364 140.972  39.799  1.00 43.14      A    C
ATOM    579  O   LEU A  78      77.499 141.975  39.088  1.00 42.76      A    O
ATOM    580  N   ARG A  79      76.170 140.474  40.086  1.00 43.08      A    N
ATOM    581  CA  ARG A  79      75.001 141.137  39.514  1.00 42.41      A    C
ATOM    582  CB  ARG A  79      73.702 140.469  39.947  1.00 43.39      A    C
ATOM    583  CG  ARG A  79      73.389 140.607  41.390  1.00 46.36      A    C
ATOM    584  CD  ARG A  79      72.073 139.959  41.705  1.00 46.57      A    C
ATOM    585  NE  ARG A  79      71.819 140.083  43.127  1.00 51.24      A    N
ATOM    586  CZ  ARG A  79      70.991 139.308  43.803  1.00 51.72      A    C
ATOM    587  NH1 ARG A  79      70.336 138.344  43.171  1.00 53.45      A    N
ATOM    588  NH2 ARG A  79      70.824 139.500  45.107  1.00 53.22      A    N
ATOM    589  C   ARG A  79      74.994 142.609  39.872  1.00 39.98      A    C
ATOM    590  O   ARG A  79      75.154 142.990  41.028  1.00 39.44      A    O
ATOM    591  N   PRO A  80      74.855 143.462  38.855  1.00 39.49      A    N
ATOM    592  CD  PRO A  80      74.965 143.088  37.430  1.00 38.66      A    C
ATOM    593  CA  PRO A  80      74.832 144.914  39.016  1.00 37.79      A    C
ATOM    594  CB  PRO A  80      75.444 145.395  37.710  1.00 39.31      A    C
ATOM    595  CG  PRO A  80      74.850 144.428  36.720  1.00 37.47      A    C
ATOM    596  C   PRO A  80      73.419 145.450  39.234  1.00 38.95      A    C
ATOM    597  O   PRO A  80      73.237 146.602  39.631  1.00 38.69      A    O
ATOM    598  N   GLU A  81      72.429 144.598  38.980  1.00 37.11      A    N
ATOM    599  CA  GLU A  81      71.026 144.958  39.128  1.00 37.06      A    C
ATOM    600  CB  GLU A  81      70.581 145.808  37.949  1.00 36.64      A    C
ATOM    601  CG  GLU A  81      70.767 145.076  36.637  1.00 38.35      A    C
ATOM    602  CD  GLU A  81      70.056 145.749  35.505  1.00 40.49      A    C
ATOM    603  OE1 GLU A  81      70.357 146.934  35.261  1.00 43.38      A    O
ATOM    604  OE2 GLU A  81      69.197 145.094  34.864  1.00 42.92      A    O
ATOM    605  C   GLU A  81      70.201 143.674  39.150  1.00 35.46      A    C
ATOM    606  O   GLU A  81      70.723 142.590  38.920  1.00 33.58      A    O
ATOM    607  N   GLY A  82      68.906 143.807  39.404  1.00 36.72      A    N
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FIGURE 11-20

ATOM	608	CA	GLY	A	82	68.049	142.638	39.467	1.00	37.51	A	C
ATOM	609	C	GLY	A	82	67.321	142.260	38.185	1.00	37.21	A	C
ATOM	610	O	GLY	A	82	67.137	141.075	37.907	1.00	39.76	A	O
ATOM	611	N	THR	A	83	66.929	143.254	37.397	1.00	37.92	A	N
ATOM	612	CA	THR	A	83	66.185	143.020	36.162	1.00	37.68	A	C
ATOM	613	CB	THR	A	83	65.933	144.337	35.444	1.00	36.95	A	C
ATOM	614	OG1	THR	A	83	65.226	145.209	36.331	1.00	35.20	A	O
ATOM	615	CG2	THR	A	83	65.091	144.124	34.200	1.00	37.74	A	C
ATOM	616	C	THR	A	83	66.798	142.023	35.193	1.00	38.32	A	C
ATOM	617	O	THR	A	83	66.233	140.952	34.971	1.00	39.13	A	O
ATOM	618	N	ALA	A	84	67.951	142.366	34.623	1.00	40.89	A	N
ATOM	619	CA	ALA	A	84	68.643	141.484	33.673	1.00	38.99	A	C
ATOM	620	CB	ALA	A	84	70.045	142.024	33.390	1.00	37.18	A	C
ATOM	621	C	ALA	A	84	68.727	140.030	34.154	1.00	38.52	A	C
ATOM	622	O	ALA	A	84	68.318	139.112	33.446	1.00	39.76	A	O
ATOM	623	N	PRO	A	85	69.255	139.803	35.367	1.00	37.87	A	N
ATOM	624	CD	PRO	A	85	69.803	140.782	36.317	1.00	37.28	A	C
ATOM	625	CA	PRO	A	85	69.374	138.446	35.904	1.00	38.12	A	C
ATOM	626	CB	PRO	A	85	69.926	138.675	37.304	1.00	36.56	A	C
ATOM	627	CG	PRO	A	85	70.715	139.927	37.144	1.00	38.37	A	C
ATOM	628	C	PRO	A	85	68.017	137.775	35.950	1.00	40.05	A	C
ATOM	629	O	PRO	A	85	67.896	136.571	35.752	1.00	43.83	A	O
ATOM	630	N	ILE	A	86	66.986	138.556	36.229	1.00	40.14	A	N
ATOM	631	CA	ILE	A	86	65.657	137.992	36.290	1.00	40.04	A	C
ATOM	632	CB	ILE	A	86	64.708	138.938	37.050	1.00	39.41	A	C
ATOM	633	CG2	ILE	A	86	63.256	138.661	36.686	1.00	38.53	A	C
ATOM	634	CG1	ILE	A	86	64.955	138.746	38.551	1.00	39.45	A	C
ATOM	635	CD1	ILE	A	86	64.238	139.711	39.426	1.00	39.24	A	C
ATOM	636	C	ILE	A	86	65.171	137.696	34.883	1.00	38.84	A	C
ATOM	637	O	ILE	A	86	64.426	136.751	34.667	1.00	36.71	A	O
ATOM	638	N	VAL	A	87	65.605	138.497	33.922	1.00	40.62	A	N
ATOM	639	CA	VAL	A	87	65.227	138.251	32.542	1.00	42.66	A	C
ATOM	640	CB	VAL	A	87	65.623	139.430	31.631	1.00	42.87	A	C
ATOM	641	CG1	VAL	A	87	65.293	139.096	30.152	1.00	43.94	A	C
ATOM	642	CG2	VAL	A	87	64.867	140.684	32.070	1.00	41.19	A	C
ATOM	643	C	VAL	A	87	65.947	136.972	32.084	1.00	43.11	A	C
ATOM	644	O	VAL	A	87	65.368	136.134	31.390	1.00	43.67	A	O
ATOM	645	N	ARG	A	88	67.197	136.808	32.506	1.00	43.18	A	N
ATOM	646	CA	ARG	A	88	67.978	135.630	32.132	1.00	43.18	A	C
ATOM	647	CB	ARG	A	88	69.432	135.787	32.613	1.00	42.58	A	C
ATOM	648	CG	ARG	A	88	70.412	134.684	32.176	1.00	40.67	A	C
ATOM	649	CD	ARG	A	88	70.340	133.479	33.096	1.00	40.90	A	C
ATOM	650	NE	ARG	A	88	70.553	133.885	34.482	1.00	43.46	A	N
ATOM	651	CZ	ARG	A	88	70.084	133.233	35.540	1.00	42.32	A	C
ATOM	652	NH1	ARG	A	88	69.372	132.126	35.374	1.00	40.20	A	N
ATOM	653	NH2	ARG	A	88	70.296	133.711	36.763	1.00	41.73	A	N
ATOM	654	C	ARG	A	88	67.327	134.397	32.753	1.00	45.04	A	C
ATOM	655	O	ARG	A	88	67.286	133.329	32.140	1.00	46.21	A	O
ATOM	656	N	ALA	A	89	66.817	134.544	33.973	1.00	43.99	A	N
ATOM	657	CA	ALA	A	89	66.152	133.440	34.653	1.00	42.38	A	C
ATOM	658	CB	ALA	A	89	65.946	133.779	36.120	1.00	43.73	A	C
ATOM	659	C	ALA	A	89	64.804	133.154	33.985	1.00	41.45	A	C
ATOM	660	O	ALA	A	89	64.428	132.003	33.809	1.00	41.84	A	O
ATOM	661	N	PHE	A	90	64.086	134.212	33.619	1.00	41.78	A	N
ATOM	662	CA	PHE	A	90	62.785	134.099	32.955	1.00	41.56	A	C
ATOM	663	CB	PHE	A	90	62.292	135.500	32.572	1.00	38.65	A	C
ATOM	664	CG	PHE	A	90	60.939	135.525	31.910	1.00	36.90	A	C
ATOM	665	CD1	PHE	A	90	59.803	135.122	32.597	1.00	37.70	A	C
ATOM	666	CD2	PHE	A	90	60.795	135.996	30.611	1.00	38.67	A	C
ATOM	667	CE1	PHE	A	90	58.537	135.190	32.005	1.00	33.89	A	C
ATOM	668	CE2	PHE	A	90	59.534	136.067	30.007	1.00	36.35	A	C

FIGURE 11-21

```
ATOM    669  CZ  PHE A  90      58.407 135.664  30.712  1.00 35.92      A    C
ATOM    670  C   PHE A  90      62.930 133.232  31.689  1.00 43.47      A    C
ATOM    671  O   PHE A  90      62.259 132.209  31.528  1.00 42.78      A    O
ATOM    672  N   VAL A  91      63.822 133.661  30.803  1.00 45.03      A    N
ATOM    673  CA  VAL A  91      64.094 132.974  29.553  1.00 47.00      A    C
ATOM    674  CB  VAL A  91      65.094 133.787  28.704  1.00 47.50      A    C
ATOM    675  CG1 VAL A  91      65.420 133.042  27.412  1.00 47.83      A    C
ATOM    676  CG2 VAL A  91      64.509 135.155  28.399  1.00 44.69      A    C
ATOM    677  C   VAL A  91      64.651 131.558  29.742  1.00 49.72      A    C
ATOM    678  O   VAL A  91      64.117 130.595  29.181  1.00 50.05      A    O
ATOM    679  N   GLU A  92      65.714 131.435  30.534  1.00 49.69      A    N
ATOM    680  CA  GLU A  92      66.346 130.144  30.772  1.00 51.75      A    C
ATOM    681  CB  GLU A  92      67.538 130.320  31.718  1.00 55.02      A    C
ATOM    682  CG  GLU A  92      68.173 129.020  32.194  1.00 60.90      A    C
ATOM    683  CD  GLU A  92      69.341 129.242  33.159  1.00 64.75      A    C
ATOM    684  OE1 GLU A  92      69.687 128.299  33.905  1.00 66.65      A    O
ATOM    685  OE2 GLU A  92      69.919 130.352  33.166  1.00 66.37      A    O
ATOM    686  C   GLU A  92      65.411 129.050  31.296  1.00 52.12      A    C
ATOM    687  O   GLU A  92      65.566 127.882  30.933  1.00 53.77      A    O
ATOM    688  N   ASN A  93      64.445 129.412  32.135  1.00 49.95      A    N
ATOM    689  CA  ASN A  93      63.509 128.427  32.679  1.00 48.69      A    C
ATOM    690  CB  ASN A  93      63.259 128.696  34.162  1.00 49.58      A    C
ATOM    691  CG  ASN A  93      64.523 128.579  34.992  1.00 50.85      A    C
ATOM    692  OD1 ASN A  93      64.983 127.481  35.284  1.00 50.36      A    O
ATOM    693  ND2 ASN A  93      65.099 129.716  35.358  1.00 48.96      A    N
ATOM    694  C   ASN A  93      62.192 128.457  31.923  1.00 49.28      A    C
ATOM    695  O   ASN A  93      61.206 127.845  32.335  1.00 47.36      A    O
ATOM    696  N   LYS A  94      62.182 129.179  30.810  1.00 49.65      A    N
ATOM    697  CA  LYS A  94      60.987 129.275  29.986  1.00 52.68      A    C
ATOM    698  CB  LYS A  94      60.784 127.963  29.219  1.00 54.58      A    C
ATOM    699  CG  LYS A  94      61.979 127.580  28.353  1.00 56.15      A    C
ATOM    700  CD  LYS A  94      61.739 126.292  27.586  1.00 56.76      A    C
ATOM    701  CE  LYS A  94      62.888 126.010  26.624  1.00 56.17      A    C
ATOM    702  NZ  LYS A  94      62.681 124.743  25.858  1.00 56.46      A    N
ATOM    703  C   LYS A  94      59.751 129.585  30.815  1.00 51.96      A    C
ATOM    704  O   LYS A  94      58.737 128.912  30.705  1.00 53.15      A    O
ATOM    705  N   LEU A  95      59.838 130.616  31.643  1.00 52.49      A    N
ATOM    706  CA  LEU A  95      58.717 131.003  32.486  1.00 50.57      A    C
ATOM    707  CB  LEU A  95      59.220 131.906  33.618  1.00 51.17      A    C
ATOM    708  CG  LEU A  95      60.309 131.238  34.458  1.00 51.42      A    C
ATOM    709  CD1 LEU A  95      60.802 132.176  35.544  1.00 50.31      A    C
ATOM    710  CD2 LEU A  95      59.744 129.957  35.070  1.00 52.72      A    C
ATOM    711  C   LEU A  95      57.644 131.705  31.652  1.00 50.22      A    C
ATOM    712  O   LEU A  95      56.584 132.085  32.153  1.00 49.30      A    O
ATOM    713  N   TYR A  96      57.928 131.885  30.370  1.00 50.26      A    N
ATOM    714  CA  TYR A  96      56.966 132.510  29.472  1.00 51.56      A    C
ATOM    715  CB  TYR A  96      57.702 133.176  28.316  1.00 50.88      A    C
ATOM    716  CG  TYR A  96      58.690 132.256  27.633  1.00 51.47      A    C
ATOM    717  CD1 TYR A  96      58.269 131.310  26.691  1.00 52.17      A    C
ATOM    718  CE1 TYR A  96      59.181 130.444  26.079  1.00 51.55      A    C
ATOM    719  CD2 TYR A  96      60.044 132.312  27.946  1.00 51.61      A    C
ATOM    720  CE2 TYR A  96      60.960 131.454  27.345  1.00 52.55      A    C
ATOM    721  CZ  TYR A  96      60.523 130.526  26.411  1.00 52.91      A    C
ATOM    722  OH  TYR A  96      61.440 129.699  25.806  1.00 54.53      A    O
ATOM    723  C   TYR A  96      56.055 131.405  28.943  1.00 53.26      A    C
ATOM    724  O   TYR A  96      55.007 131.672  28.361  1.00 52.62      A    O
ATOM    725  N   GLY A  97      56.476 130.161  29.166  1.00 55.33      A    N
ATOM    726  CA  GLY A  97      55.731 129.003  28.706  1.00 58.87      A    C
ATOM    727  C   GLY A  97      54.255 128.950  29.052  1.00 61.42      A    C
ATOM    728  O   GLY A  97      53.787 129.685  29.920  1.00 63.37      A    O
ATOM    729  N   PRO A  98      53.491 128.072  28.381  1.00 62.59      A    N
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FIGURE 11-22

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ATOM    730  CD  PRO A  98      53.934 127.241  27.248  1.00 62.83      A    C
ATOM    731  CA  PRO A  98      52.051 127.910  28.604  1.00 62.87      A    C
ATOM    732  CB  PRO A  98      51.659 126.847  27.578  1.00 61.71      A    C
ATOM    733  CG  PRO A  98      52.653 127.064  26.471  1.00 62.75      A    C
ATOM    734  C   PRO A  98      51.738 127.462  30.021  1.00 62.46      A    C
ATOM    735  O   PRO A  98      50.676 127.764  30.561  1.00 61.69      A    O
ATOM    736  N   GLU A  99      52.675 126.733  30.613  1.00 62.65      A    N
ATOM    737  CA  GLU A  99      52.509 126.218  31.964  1.00 63.50      A    C
ATOM    738  CB  GLU A  99      53.689 125.295  32.309  1.00 67.79      A    C
ATOM    739  CG  GLU A  99      53.579 124.568  33.652  1.00 70.48      A    C
ATOM    740  CD  GLU A  99      54.934 124.096  34.169  1.00 74.31      A    C
ATOM    741  OE1 GLU A  99      55.677 123.438  33.398  1.00 73.53      A    O
ATOM    742  OE2 GLU A  99      55.254 124.388  35.350  1.00 74.17      A    O
ATOM    743  C   GLU A  99      52.424 127.341  33.000  1.00 62.31      A    C
ATOM    744  O   GLU A  99      51.862 127.155  34.086  1.00 60.75      A    O
ATOM    745  N   TYR A 100      52.969 128.508  32.661  1.00 59.71      A    N
ATOM    746  CA  TYR A 100      52.983 129.613  33.605  1.00 57.19      A    C
ATOM    747  CB  TYR A 100      54.388 130.205  33.693  1.00 53.48      A    C
ATOM    748  CG  TYR A 100      55.426 129.181  34.055  1.00 52.74      A    C
ATOM    749  CD1 TYR A 100      56.173 128.539  33.062  1.00 53.18      A    C
ATOM    750  CE1 TYR A 100      57.115 127.564  33.385  1.00 52.33      A    C
ATOM    751  CD2 TYR A 100      55.644 128.821  35.388  1.00 50.62      A    C
ATOM    752  CE2 TYR A 100      56.584 127.840  35.727  1.00 51.49      A    C
ATOM    753  CZ  TYR A 100      57.317 127.219  34.719  1.00 53.55      A    C
ATOM    754  OH  TYR A 100      58.261 126.265  35.039  1.00 56.01      A    O
ATOM    755  C   TYR A 100      51.987 130.734  33.420  1.00 56.83      A    C
ATOM    756  O   TYR A 100      51.568 131.067  32.307  1.00 55.46      A    O
ATOM    757  N   THR A 101      51.630 131.311  34.561  1.00 56.39      A    N
ATOM    758  CA  THR A 101      50.696 132.420  34.659  1.00 55.80      A    C
ATOM    759  CB  THR A 101      50.524 132.825  36.142  1.00 57.47      A    C
ATOM    760  OG1 THR A 101      49.852 134.089  36.228  1.00 59.98      A    O
ATOM    761  CG2 THR A 101      51.885 132.918  36.825  1.00 57.03      A    C
ATOM    762  C   THR A 101      51.136 133.649  33.864  1.00 52.79      A    C
ATOM    763  O   THR A 101      52.322 133.951  33.753  1.00 49.92      A    O
ATOM    764  N   LYS A 102      50.156 134.345  33.307  1.00 51.37      A    N
ATOM    765  CA  LYS A 102      50.395 135.552  32.542  1.00 50.10      A    C
ATOM    766  CB  LYS A 102      49.954 135.379  31.083  1.00 54.57      A    C
ATOM    767  CG  LYS A 102      51.032 134.942  30.087  1.00 55.76      A    C
ATOM    768  CD  LYS A 102      51.512 133.519  30.323  1.00 58.52      A    C
ATOM    769  CE  LYS A 102      52.245 132.970  29.086  1.00 58.16      A    C
ATOM    770  NZ  LYS A 102      53.140 133.990  28.447  1.00 58.16      A    N
ATOM    771  C   LYS A 102      49.568 136.667  33.175  1.00 48.26      A    C
ATOM    772  O   LYS A 102      48.352 136.532  33.338  1.00 47.64      A    O
ATOM    773  N   PRO A 103      50.221 137.776  33.558  1.00 45.65      A    N
ATOM    774  CD  PRO A 103      49.575 139.040  33.955  1.00 45.23      A    C
ATOM    775  CA  PRO A 103      51.668 137.954  33.399  1.00 42.79      A    C
ATOM    776  CB  PRO A 103      51.829 139.470  33.434  1.00 44.42      A    C
ATOM    777  CG  PRO A 103      50.758 139.896  34.372  1.00 45.08      A    C
ATOM    778  C   PRO A 103      52.441 137.250  34.515  1.00 39.29      A    C
ATOM    779  O   PRO A 103      51.890 136.985  35.579  1.00 38.36      A    O
ATOM    780  N   TYR A 104      53.697 136.907  34.260  1.00 35.50      A    N
ATOM    781  CA  TYR A 104      54.506 136.259  35.284  1.00 35.88      A    C
ATOM    782  CB  TYR A 104      55.719 135.567  34.656  1.00 35.42      A    C
ATOM    783  CG  TYR A 104      56.417 134.614  35.599  1.00 37.88      A    C
ATOM    784  CD1 TYR A 104      55.862 133.372  35.908  1.00 39.09      A    C
ATOM    785  CE1 TYR A 104      56.498 132.496  36.808  1.00 40.87      A    C
ATOM    786  CD2 TYR A 104      57.622 134.962  36.207  1.00 38.42      A    C
ATOM    787  CE2 TYR A 104      58.265 134.096  37.104  1.00 38.54      A    C
ATOM    788  CZ  TYR A 104      57.704 132.870  37.396  1.00 40.90      A    C
ATOM    789  OH  TYR A 104      58.370 132.003  38.239  1.00 43.38      A    O
ATOM    790  C   TYR A 104      54.949 137.383  36.227  1.00 36.00      A    C
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FIGURE 11-23

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ATOM    791  O   TYR A 104      55.760 138.238  35.860  1.00 36.16      A    O
ATOM    792  N   LYS A 105      54.391 137.374  37.435  1.00 36.89      A    N
ATOM    793  CA  LYS A 105      54.645 138.394  38.450  1.00 35.81      A    C
ATOM    794  CB  LYS A 105      53.374 138.650  39.256  1.00 35.04      A    C
ATOM    795  CG  LYS A 105      52.283 139.389  38.502  1.00 35.93      A    C
ATOM    796  CD  LYS A 105      51.077 139.613  39.422  1.00 36.42      A    C
ATOM    797  CE  LYS A 105      50.172 140.692  38.892  1.00 37.80      A    C
ATOM    798  NZ  LYS A 105      49.108 141.009  39.881  1.00 42.68      A    N
ATOM    799  C   LYS A 105      55.762 138.034  39.406  1.00 35.40      A    C
ATOM    800  O   LYS A 105      55.606 137.178  40.271  1.00 35.69      A    O
ATOM    801  N   THR A 106      56.878 138.731  39.286  1.00 36.54      A    N
ATOM    802  CA  THR A 106      58.003 138.425  40.138  1.00 36.40      A    C
ATOM    803  CB  THR A 106      59.075 137.715  39.320  1.00 38.15      A    C
ATOM    804  OG1 THR A 106      60.034 137.132  40.209  1.00 43.31      A    O
ATOM    805  CG2 THR A 106      59.753 138.691  38.380  1.00 36.83      A    C
ATOM    806  C   THR A 106      58.606 139.638  40.839  1.00 34.46      A    C
ATOM    807  O   THR A 106      58.363 140.779  40.465  1.00 34.35      A    O
ATOM    808  N   TYR A 107      59.376 139.385  41.885  1.00 33.98      A    N
ATOM    809  CA  TYR A 107      60.009 140.462  42.617  1.00 33.99      A    C
ATOM    810  CB  TYR A 107      59.078 140.989  43.721  1.00 34.36      A    C
ATOM    811  CG  TYR A 107      59.033 140.188  45.009  1.00 36.34      A    C
ATOM    812  CD1 TYR A 107      60.118 140.185  45.893  1.00 35.87      A    C
ATOM    813  CE1 TYR A 107      60.065 139.490  47.097  1.00 36.55      A    C
ATOM    814  CD2 TYR A 107      57.888 139.465  45.367  1.00 36.87      A    C
ATOM    815  CE2 TYR A 107      57.824 138.762  46.569  1.00 35.62      A    C
ATOM    816  CZ  TYR A 107      58.919 138.781  47.430  1.00 37.27      A    C
ATOM    817  OH  TYR A 107      58.873 138.102  48.630  1.00 40.77      A    O
ATOM    818  C   TYR A 107      61.311 139.953  43.201  1.00 33.89      A    C
ATOM    819  O   TYR A 107      61.479 138.753  43.372  1.00 32.98      A    O
ATOM    820  N   TYR A 108      62.244 140.856  43.474  1.00 33.63      A    N
ATOM    821  CA  TYR A 108      63.512 140.443  44.048  1.00 34.09      A    C
ATOM    822  CB  TYR A 108      64.616 140.377  42.984  1.00 33.78      A    C
ATOM    823  CG  TYR A 108      64.893 141.704  42.345  1.00 36.25      A    C
ATOM    824  CD1 TYR A 108      64.182 142.112  41.217  1.00 36.47      A    C
ATOM    825  CE1 TYR A 108      64.369 143.376  40.668  1.00 37.55      A    C
ATOM    826  CD2 TYR A 108      65.809 142.594  42.912  1.00 32.44      A    C
ATOM    827  CE2 TYR A 108      66.001 143.859  42.375  1.00 35.20      A    C
ATOM    828  CZ  TYR A 108      65.272 144.245  41.254  1.00 37.49      A    C
ATOM    829  OH  TYR A 108      65.403 145.516  40.748  1.00 42.00      A    O
ATOM    830  C   TYR A 108      63.896 141.415  45.154  1.00 33.58      A    C
ATOM    831  O   TYR A 108      63.404 142.540  45.221  1.00 31.68      A    O
ATOM    832  N   MET A 109      64.799 140.974  46.009  1.00 34.48      A    N
ATOM    833  CA  MET A 109      65.213 141.765  47.143  1.00 35.06      A    C
ATOM    834  CB  MET A 109      64.260 141.432  48.274  1.00 38.87      A    C
ATOM    835  CG  MET A 109      64.073 142.445  49.352  1.00 42.71      A    C
ATOM    836  SD  MET A 109      62.765 141.752  50.407  1.00 48.26      A    S
ATOM    837  CE  MET A 109      61.356 142.340  49.570  1.00 41.35      A    C
ATOM    838  C   MET A 109      66.629 141.295  47.469  1.00 36.21      A    C
ATOM    839  O   MET A 109      66.831 140.158  47.882  1.00 33.91      A    O
ATOM    840  N   GLY A 110      67.618 142.152  47.264  1.00 37.08      A    N
ATOM    841  CA  GLY A 110      68.966 141.727  47.556  1.00 34.80      A    C
ATOM    842  C   GLY A 110      70.074 142.666  47.136  1.00 35.78      A    C
ATOM    843  O   GLY A 110      69.855 143.678  46.455  1.00 34.75      A    O
ATOM    844  N   PRO A 111      71.305 142.329  47.532  1.00 34.74      A    N
ATOM    845  CD  PRO A 111      71.680 141.096  48.242  1.00 32.63      A    C
ATOM    846  CA  PRO A 111      72.486 143.124  47.214  1.00 34.82      A    C
ATOM    847  CB  PRO A 111      73.582 142.440  48.027  1.00 34.63      A    C
ATOM    848  CG  PRO A 111      73.172 141.020  47.975  1.00 33.98      A    C
ATOM    849  C   PRO A 111      72.810 143.144  45.722  1.00 35.83      A    C
ATOM    850  O   PRO A 111      72.577 142.173  45.009  1.00 36.25      A    O
ATOM    851  N   MET A 112      73.321 144.280  45.270  1.00 34.53      A    N
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FIGURE 11-24

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ATOM    852  CA  MET A 112      73.750 144.461  43.894  1.00 37.54      A    C
ATOM    853  CB  MET A 112      72.875 145.478  43.161  1.00 37.24      A    C
ATOM    854  CG  MET A 112      71.432 145.035  42.997  1.00 38.68      A    C
ATOM    855  SD  MET A 112      71.290 143.433  42.188  1.00 40.03      A    S
ATOM    856  CE  MET A 112      69.610 142.923  42.633  1.00 32.92      A    C
ATOM    857  C   MET A 112      75.172 144.995  44.047  1.00 38.95      A    C
ATOM    858  O   MET A 112      75.546 145.500  45.114  1.00 37.77      A    O
ATOM    859  N   PHE A 113      75.965 144.879  42.993  1.00 40.21      A    N
ATOM    860  CA  PHE A 113      77.341 145.321  43.067  1.00 41.56      A    C
ATOM    861  CB  PHE A 113      78.249 144.094  43.160  1.00 38.41      A    C
ATOM    862  CG  PHE A 113      77.902 143.183  44.306  1.00 33.77      A    C
ATOM    863  CD1 PHE A 113      78.480 143.364  45.556  1.00 32.45      A    C
ATOM    864  CD2 PHE A 113      76.955 142.178  44.146  1.00 31.55      A    C
ATOM    865  CE1 PHE A 113      78.123 142.560  46.638  1.00 30.29      A    C
ATOM    866  CE2 PHE A 113      76.588 141.368  45.218  1.00 31.50      A    C
ATOM    867  CZ  PHE A 113      77.178 141.561  46.474  1.00 31.15      A    C
ATOM    868  C   PHE A 113      77.711 146.184  41.885  1.00 44.67      A    C
ATOM    869  O   PHE A 113      77.195 145.998  40.783  1.00 44.98      A    O
ATOM    870  N   ARG A 114      78.594 147.144  42.141  1.00 48.65      A    N
ATOM    871  CA  ARG A 114      79.076 148.077  41.133  1.00 52.97      A    C
ATOM    872  CB  ARG A 114      78.036 149.180  40.874  1.00 54.47      A    C
ATOM    873  CG  ARG A 114      76.817 148.724  40.049  1.00 58.74      A    C
ATOM    874  CD  ARG A 114      75.796 149.851  39.844  1.00 60.26      A    C
ATOM    875  NE  ARG A 114      74.550 149.376  39.233  1.00 62.60      A    N
ATOM    876  CZ  ARG A 114      73.403 150.058  39.228  1.00 63.41      A    C
ATOM    877  NH1 ARG A 114      73.332 151.253  39.802  1.00 61.87      A    N
ATOM    878  NH2 ARG A 114      72.318 149.541  38.657  1.00 63.44      A    N
ATOM    879  C   ARG A 114      80.381 148.702  41.614  1.00 56.39      A    C
ATOM    880  O   ARG A 114      80.746 148.582  42.783  1.00 56.08      A    O
ATOM    881  N   TYR A 115      81.091 149.350  40.697  1.00 61.85      A    N
ATOM    882  CA  TYR A 115      82.349 150.025  41.014  1.00 65.12      A    C
ATOM    883  CB  TYR A 115      83.418 149.740  39.951  1.00 64.02      A    C
ATOM    884  CG  TYR A 115      84.125 148.404  40.020  1.00 62.42      A    C
ATOM    885  CD1 TYR A 115      84.202 147.585  38.891  1.00 61.89      A    C
ATOM    886  CE1 TYR A 115      84.902 146.379  38.914  1.00 61.95      A    C
ATOM    887  CD2 TYR A 115      84.767 147.982  41.184  1.00 62.20      A    C
ATOM    888  CE2 TYR A 115      85.473 146.774  41.218  1.00 62.56      A    C
ATOM    889  CZ  TYR A 115      85.536 145.980  40.077  1.00 62.46      A    C
ATOM    890  OH  TYR A 115      86.245 144.799  40.090  1.00 62.21      A    O
ATOM    891  C   TYR A 115      82.092 151.527  41.005  1.00 69.37      A    C
ATOM    892  O   TYR A 115      81.068 152.000  40.499  1.00 67.95      A    O
ATOM    893  N   GLU A 116      83.043 152.272  41.554  1.00 75.47      A    N
ATOM    894  CA  GLU A 116      82.967 153.728  41.582  1.00 79.71      A    C
ATOM    895  CB  GLU A 116      83.540 154.244  42.900  1.00 81.77      A    C
ATOM    896  CG  GLU A 116      82.710 153.825  44.098  1.00 84.64      A    C
ATOM    897  CD  GLU A 116      81.275 154.307  43.983  1.00 86.90      A    C
ATOM    898  OE1 GLU A 116      81.071 155.541  43.929  1.00 87.44      A    O
ATOM    899  OE2 GLU A 116      80.357 153.457  43.937  1.00 87.20      A    O
ATOM    900  C   GLU A 116      83.771 154.259  40.390  1.00 81.54      A    C
ATOM    901  O   GLU A 116      84.557 155.204  40.512  1.00 81.54      A    O
ATOM    902  N   ARG A 117      83.562 153.623  39.237  1.00 83.80      A    N
ATOM    903  CA  ARG A 117      84.244 153.978  37.995  1.00 85.76      A    C
ATOM    904  CB  ARG A 117      85.130 152.816  37.527  1.00 86.12      A    C
ATOM    905  CG  ARG A 117      86.124 152.314  38.564  1.00 87.37      A    C
ATOM    906  CD  ARG A 117      86.765 151.011  38.102  1.00 88.50      A    C
ATOM    907  NE  ARG A 117      87.606 150.400  39.130  1.00 89.21      A    N
ATOM    908  CZ  ARG A 117      88.045 149.144  39.083  1.00 89.90      A    C
ATOM    909  NH1 ARG A 117      87.723 148.366  38.058  1.00 89.45      A    N
ATOM    910  NH2 ARG A 117      88.800 148.659  40.061  1.00 90.29      A    N
ATOM    911  C   ARG A 117      83.215 154.296  36.909  1.00 86.34      A    C
ATOM    912  O   ARG A 117      83.040 153.529  35.958  1.00 86.31      A    O
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FIGURE 11-25

ATOM	913	N	ARG	A	122	86.378	151.624	43.326	1.00	75.34	A	N
ATOM	914	CA	ARG	A	122	86.172	150.750	44.479	1.00	75.88	A	C
ATOM	915	CB	ARG	A	122	86.217	151.559	45.779	1.00	78.47	A	C
ATOM	916	CG	ARG	A	122	85.969	150.718	47.027	1.00	82.63	A	C
ATOM	917	CD	ARG	A	122	85.946	151.572	48.287	1.00	85.77	A	C
ATOM	918	NE	ARG	A	122	85.644	150.781	49.477	1.00	87.82	A	N
ATOM	919	CZ	ARG	A	122	85.682	151.256	50.719	1.00	89.64	A	C
ATOM	920	NH1	ARG	A	122	86.013	152.523	50.938	1.00	90.31	A	N
ATOM	921	NH2	ARG	A	122	85.384	150.466	51.745	1.00	90.24	A	N
ATOM	922	C	ARG	A	122	84.842	149.992	44.403	1.00	74.09	A	C
ATOM	923	O	ARG	A	122	83.845	150.506	43.876	1.00	74.07	A	O
ATOM	924	N	LEU	A	123	84.839	148.776	44.948	1.00	69.99	A	N
ATOM	925	CA	LEU	A	123	83.661	147.916	44.949	1.00	65.93	A	C
ATOM	926	CB	LEU	A	123	84.071	146.469	45.248	1.00	66.17	A	C
ATOM	927	CG	LEU	A	123	82.932	145.453	45.380	1.00	66.85	A	C
ATOM	928	CD1	LEU	A	123	82.094	145.464	44.115	1.00	66.51	A	C
ATOM	929	CD2	LEU	A	123	83.495	144.064	45.640	1.00	66.88	A	C
ATOM	930	C	LEU	A	123	82.603	148.349	45.957	1.00	62.85	A	C
ATOM	931	O	LEU	A	123	82.893	148.487	47.145	1.00	62.55	A	O
ATOM	932	N	ARG	A	124	81.379	148.560	45.478	1.00	57.65	A	N
ATOM	933	CA	ARG	A	124	80.278	148.953	46.347	1.00	53.23	A	C
ATOM	934	CB	ARG	A	124	79.790	150.363	46.013	1.00	55.67	A	C
ATOM	935	CG	ARG	A	124	80.481	151.447	46.819	1.00	62.01	A	C
ATOM	936	CD	ARG	A	124	79.832	152.796	46.605	1.00	65.84	A	C
ATOM	937	NE	ARG	A	124	78.403	152.773	46.915	1.00	71.69	A	N
ATOM	938	CZ	ARG	A	124	77.603	153.835	46.823	1.00	73.11	A	C
ATOM	939	NH1	ARG	A	124	78.093	155.004	46.428	1.00	72.36	A	N
ATOM	940	NH2	ARG	A	124	76.314	153.733	47.126	1.00	73.01	A	N
ATOM	941	C	ARG	A	124	79.091	147.996	46.314	1.00	48.40	A	C
ATOM	942	O	ARG	A	124	78.638	147.563	45.250	1.00	43.56	A	O
ATOM	943	N	GLN	A	125	78.604	147.672	47.507	1.00	43.67	A	N
ATOM	944	CA	GLN	A	125	77.462	146.798	47.663	1.00	40.10	A	C
ATOM	945	CB	GLN	A	125	77.716	145.756	48.744	1.00	38.76	A	C
ATOM	946	CG	GLN	A	125	76.502	144.877	48.983	1.00	38.55	A	C
ATOM	947	CD	GLN	A	125	76.765	143.742	49.940	1.00	38.37	A	C
ATOM	948	OE1	GLN	A	125	77.858	143.179	49.963	1.00	41.41	A	O
ATOM	949	NE2	GLN	A	125	75.754	143.377	50.720	1.00	36.72	A	N
ATOM	950	C	GLN	A	125	76.263	147.617	48.084	1.00	39.71	A	C
ATOM	951	O	GLN	A	125	76.273	148.189	49.178	1.00	40.48	A	O
ATOM	952	N	PHE	A	126	75.247	147.696	47.222	1.00	37.20	A	N
ATOM	953	CA	PHE	A	126	74.009	148.412	47.563	1.00	34.66	A	C
ATOM	954	CB	PHE	A	126	73.758	149.594	46.623	1.00	33.55	A	C
ATOM	955	CG	PHE	A	126	73.739	149.231	45.161	1.00	34.00	A	C
ATOM	956	CD1	PHE	A	126	74.901	148.795	44.519	1.00	34.95	A	C
ATOM	957	CD2	PHE	A	126	72.577	149.374	44.415	1.00	33.63	A	C
ATOM	958	CE1	PHE	A	126	74.905	148.515	43.157	1.00	35.07	A	C
ATOM	959	CE2	PHE	A	126	72.565	149.095	43.050	1.00	34.69	A	C
ATOM	960	CZ	PHE	A	126	73.731	148.667	42.418	1.00	34.61	A	C
ATOM	961	C	PHE	A	126	72.833	147.429	47.518	1.00	34.00	A	C
ATOM	962	O	PHE	A	126	72.968	146.317	47.019	1.00	33.58	A	O
ATOM	963	N	HIS	A	127	71.676	147.830	48.029	1.00	33.74	A	N
ATOM	964	CA	HIS	A	127	70.548	146.912	48.046	1.00	31.63	A	C
ATOM	965	CB	HIS	A	127	70.262	146.524	49.501	1.00	29.34	A	C
ATOM	966	CG	HIS	A	127	71.474	145.983	50.200	1.00	28.86	A	C
ATOM	967	CD2	HIS	A	127	71.867	144.710	50.450	1.00	26.68	A	C
ATOM	968	ND1	HIS	A	127	72.513	146.791	50.619	1.00	32.19	A	N
ATOM	969	CE1	HIS	A	127	73.493	146.039	51.095	1.00	27.16	A	C
ATOM	970	NE2	HIS	A	127	73.126	144.773	51.003	1.00	28.11	A	N
ATOM	971	C	HIS	A	127	69.309	147.404	47.321	1.00	30.31	A	C
ATOM	972	O	HIS	A	127	68.937	148.568	47.397	1.00	29.09	A	O
ATOM	973	N	GLN	A	128	68.680	146.492	46.596	1.00	32.38	A	N

FIGURE 11-26

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ATOM    974  CA  GLN A 128      67.512 146.844  45.816  1.00 34.17      A    C
ATOM    975  CB  GLN A 128      67.855 146.845  44.319  1.00 35.77      A    C
ATOM    976  CG  GLN A 128      69.058 147.707  43.913  1.00 42.46      A    C
ATOM    977  CD  GLN A 128      68.806 149.214  44.018  1.00 44.42      A    C
ATOM    978  OE1 GLN A 128      69.498 149.919  44.753  1.00 50.60      A    O
ATOM    979  NE2 GLN A 128      67.822 149.708  43.277  1.00 45.38      A    N
ATOM    980  C   GLN A 128      66.341 145.906  46.035  1.00 33.81      A    C
ATOM    981  O   GLN A 128      66.483 144.759  46.445  1.00 31.43      A    O
ATOM    982  N   ILE A 129      65.174 146.443  45.756  1.00 33.31      A    N
ATOM    983  CA  ILE A 129      63.934 145.716  45.834  1.00 34.68      A    C
ATOM    984  CB  ILE A 129      63.045 146.225  46.991  1.00 34.84      A    C
ATOM    985  CG2 ILE A 129      61.619 145.733  46.809  1.00 34.24      A    C
ATOM    986  CG1 ILE A 129      63.608 145.750  48.331  1.00 34.02      A    C
ATOM    987  CD1 ILE A 129      62.804 146.238  49.529  1.00 36.35      A    C
ATOM    988  C   ILE A 129      63.324 146.117  44.498  1.00 34.58      A    C
ATOM    989  O   ILE A 129      63.315 147.297  44.151  1.00 34.13      A    O
ATOM    990  N   GLY A 130      62.849 145.145  43.733  1.00 34.85      A    N
ATOM    991  CA  GLY A 130      62.252 145.475  42.458  1.00 33.27      A    C
ATOM    992  C   GLY A 130      61.237 144.449  42.022  1.00 33.17      A    C
ATOM    993  O   GLY A 130      61.180 143.339  42.556  1.00 33.58      A    O
ATOM    994  N   VAL A 131      60.410 144.830  41.059  1.00 32.57      A    N
ATOM    995  CA  VAL A 131      59.432 143.911  40.531  1.00 31.32      A    C
ATOM    996  CB  VAL A 131      57.981 144.280  40.933  1.00 31.61      A    C
ATOM    997  CG1 VAL A 131      57.844 144.334  42.458  1.00 34.43      A    C
ATOM    998  CG2 VAL A 131      57.597 145.586  40.332  1.00 29.74      A    C
ATOM    999  C   VAL A 131      59.522 143.968  39.025  1.00 31.64      A    C
ATOM   1000  O   VAL A 131      59.960 144.972  38.467  1.00 28.59      A    O
ATOM   1001  N   GLU A 132      59.118 142.869  38.392  1.00 30.94      A    N
ATOM   1002  CA  GLU A 132      59.056 142.744  36.949  1.00 33.89      A    C
ATOM   1003  CB  GLU A 132      60.305 142.047  36.387  1.00 38.15      A    C
ATOM   1004  CG  GLU A 132      61.639 142.710  36.736  1.00 40.85      A    C
ATOM   1005  CD  GLU A 132      61.806 144.075  36.106  1.00 44.28      A    C
ATOM   1006  OE1 GLU A 132      62.795 144.766  36.427  1.00 45.57      A    O
ATOM   1007  OE2 GLU A 132      60.950 144.462  35.287  1.00 47.61      A    O
ATOM   1008  C   GLU A 132      57.821 141.875  36.692  1.00 34.15      A    C
ATOM   1009  O   GLU A 132      57.648 140.824  37.321  1.00 33.37      A    O
ATOM   1010  N   ALA A 133      56.947 142.337  35.802  1.00 33.12      A    N
ATOM   1011  CA  ALA A 133      55.753 141.591  35.431  1.00 34.19      A    C
ATOM   1012  CB  ALA A 133      54.511 142.426  35.705  1.00 32.63      A    C
ATOM   1013  C   ALA A 133      55.881 141.281  33.929  1.00 35.34      A    C
ATOM   1014  O   ALA A 133      55.826 142.189  33.091  1.00 33.13      A    O
ATOM   1015  N   PHE A 134      56.074 140.011  33.585  1.00 36.95      A    N
ATOM   1016  CA  PHE A 134      56.230 139.644  32.174  1.00 40.04      A    C
ATOM   1017  CB  PHE A 134      57.378 138.652  31.980  1.00 37.55      A    C
ATOM   1018  CG  PHE A 134      58.674 139.064  32.617  1.00 39.02      A    C
ATOM   1019  CD1 PHE A 134      59.053 138.540  33.849  1.00 37.16      A    C
ATOM   1020  CD2 PHE A 134      59.550 139.912  31.957  1.00 38.40      A    C
ATOM   1021  CE1 PHE A 134      60.284 138.846  34.404  1.00 36.94      A    C
ATOM   1022  CE2 PHE A 134      60.787 140.223  32.509  1.00 39.67      A    C
ATOM   1023  CZ  PHE A 134      61.152 139.685  33.734  1.00 38.11      A    C
ATOM   1024  C   PHE A 134      55.012 139.028  31.495  1.00 41.89      A    C
ATOM   1025  O   PHE A 134      54.339 138.163  32.059  1.00 42.17      A    O
ATOM   1026  N   GLY A 135      54.742 139.471  30.271  1.00 43.96      A    N
ATOM   1027  CA  GLY A 135      53.652 138.883  29.515  1.00 44.79      A    C
ATOM   1028  C   GLY A 135      52.457 139.705  29.092  1.00 45.17      A    C
ATOM   1029  O   GLY A 135      51.842 139.405  28.068  1.00 46.97      A    O
ATOM   1030  N   SER A 136      52.118 140.737  29.855  1.00 45.10      A    N
ATOM   1031  CA  SER A 136      50.950 141.531  29.528  1.00 44.06      A    C
ATOM   1032  CB  SER A 136      50.039 141.610  30.746  1.00 42.31      A    C
ATOM   1033  OG  SER A 136      48.907 142.410  30.462  1.00 48.56      A    O
ATOM   1034  C   SER A 136      51.212 142.928  28.991  1.00 45.13      A    C
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FIGURE 11-27

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ATOM   1035  O   SER A 136      52.160 143.603  29.395  1.00 47.84      A    O
ATOM   1036  N   GLU A 137      50.347 143.359  28.080  1.00 45.54      A    N
ATOM   1037  CA  GLU A 137      50.451 144.678  27.466  1.00 46.12      A    C
ATOM   1038  CB  GLU A 137      50.255 144.553  25.950  1.00 47.65      A    C
ATOM   1039  CG  GLU A 137      51.045 145.575  25.157  1.00 55.87      A    C
ATOM   1040  CD  GLU A 137      51.225 145.201  23.694  1.00 58.48      A    C
ATOM   1041  OE1 GLU A 137      51.920 145.964  22.983  1.00 63.18      A    O
ATOM   1042  OE2 GLU A 137      50.683 144.161  23.254  1.00 58.75      A    O
ATOM   1043  C   GLU A 137      49.387 145.609  28.056  1.00 43.87      A    C
ATOM   1044  O   GLU A 137      49.378 146.814  27.795  1.00 42.99      A    O
ATOM   1045  N   ASN A 138      48.502 145.038  28.868  1.00 41.00      A    N
ATOM   1046  CA  ASN A 138      47.417 145.795  29.483  1.00 40.19      A    C
ATOM   1047  CB  ASN A 138      46.579 144.857  30.348  1.00 38.17      A    C
ATOM   1048  CG  ASN A 138      45.250 145.464  30.737  1.00 40.19      A    C
ATOM   1049  OD1 ASN A 138      45.095 146.688  30.732  1.00 39.25      A    O
ATOM   1050  ND2 ASN A 138      44.278 144.610  31.090  1.00 40.53      A    N
ATOM   1051  C   ASN A 138      47.888 147.006  30.315  1.00 39.67      A    C
ATOM   1052  O   ASN A 138      48.743 146.882  31.198  1.00 40.46      A    O
ATOM   1053  N   PRO A 139      47.330 148.196  30.045  1.00 38.48      A    N
ATOM   1054  CD  PRO A 139      46.321 148.519  29.028  1.00 36.31      A    C
ATOM   1055  CA  PRO A 139      47.724 149.400  30.792  1.00 38.18      A    C
ATOM   1056  CB  PRO A 139      46.991 150.528  30.062  1.00 37.30      A    C
ATOM   1057  CG  PRO A 139      46.656 149.941  28.729  1.00 39.86      A    C
ATOM   1058  C   PRO A 139      47.267 149.287  32.250  1.00 39.08      A    C
ATOM   1059  O   PRO A 139      47.761 149.989  33.139  1.00 36.37      A    O
ATOM   1060  N   ALA A 140      46.308 148.396  32.473  1.00 38.86      A    N
ATOM   1061  CA  ALA A 140      45.770 148.173  33.799  1.00 39.85      A    C
ATOM   1062  CB  ALA A 140      44.584 147.207  33.728  1.00 39.90      A    C
ATOM   1063  C   ALA A 140      46.870 147.608  34.691  1.00 39.76      A    C
ATOM   1064  O   ALA A 140      46.866 147.829  35.895  1.00 40.22      A    O
ATOM   1065  N   LEU A 141      47.811 146.874  34.099  1.00 39.83      A    N
ATOM   1066  CA  LEU A 141      48.912 146.304  34.870  1.00 38.77      A    C
ATOM   1067  CB  LEU A 141      49.657 145.254  34.041  1.00 39.21      A    C
ATOM   1068  CG  LEU A 141      50.757 144.450  34.744  1.00 38.42      A    C
ATOM   1069  CD1 LEU A 141      50.180 143.704  35.930  1.00 37.06      A    C
ATOM   1070  CD2 LEU A 141      51.389 143.480  33.767  1.00 38.22      A    C
ATOM   1071  C   LEU A 141      49.859 147.436  35.274  1.00 39.11      A    C
ATOM   1072  O   LEU A 141      50.358 147.464  36.403  1.00 38.85      A    O
ATOM   1073  N   ASP A 142      50.090 148.375  34.356  1.00 37.13      A    N
ATOM   1074  CA  ASP A 142      50.957 149.513  34.640  1.00 37.04      A    C
ATOM   1075  CB  ASP A 142      50.915 150.574  33.524  1.00 36.91      A    C
ATOM   1076  CG  ASP A 142      51.288 150.029  32.153  1.00 37.76      A    C
ATOM   1077  OD1 ASP A 142      51.741 150.827  31.313  1.00 38.85      A    O
ATOM   1078  OD2 ASP A 142      51.117 148.825  31.894  1.00 40.61      A    O
ATOM   1079  C   ASP A 142      50.450 150.179  35.912  1.00 36.79      A    C
ATOM   1080  O   ASP A 142      51.207 150.413  36.851  1.00 35.81      A    O
ATOM   1081  N   VAL A 143      49.160 150.494  35.928  1.00 35.33      A    N
ATOM   1082  CA  VAL A 143      48.570 151.159  37.070  1.00 35.89      A    C
ATOM   1083  CB  VAL A 143      47.141 151.589  36.760  1.00 36.79      A    C
ATOM   1084  CG1 VAL A 143      46.466 152.158  38.002  1.00 32.20      A    C
ATOM   1085  CG2 VAL A 143      47.174 152.622  35.655  1.00 34.00      A    C
ATOM   1086  C   VAL A 143      48.597 150.315  38.324  1.00 37.02      A    C
ATOM   1087  O   VAL A 143      48.774 150.841  39.423  1.00 38.33      A    O
ATOM   1088  N   GLU A 144      48.434 149.006  38.176  1.00 37.36      A    N
ATOM   1089  CA  GLU A 144      48.463 148.141  39.341  1.00 35.80      A    C
ATOM   1090  CB  GLU A 144      48.190 146.684  38.969  1.00 36.54      A    C
ATOM   1091  CG  GLU A 144      48.102 145.791  40.210  1.00 38.18      A    C
ATOM   1092  CD  GLU A 144      48.320 144.316  39.929  1.00 39.75      A    C
ATOM   1093  OE1 GLU A 144      49.460 143.926  39.576  1.00 39.81      A    O
ATOM   1094  OE2 GLU A 144      47.348 143.544  40.077  1.00 39.78      A    O
ATOM   1095  C   GLU A 144      49.843 148.212  39.991  1.00 36.75      A    C
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FIGURE 11-28

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ATOM   1096  O   GLU A 144      49.967 148.331  41.217  1.00 35.32      A    O
ATOM   1097  N   ILE A 145      50.882 148.131  39.162  1.00 32.89      A    N
ATOM   1098  CA  ILE A 145      52.229 148.150  39.685  1.00 32.81      A    C
ATOM   1099  CB  ILE A 145      53.236 147.784  38.597  1.00 30.91      A    C
ATOM   1100  CG2 ILE A 145      54.648 148.063  39.091  1.00 28.19      A    C
ATOM   1101  CG1 ILE A 145      53.047 146.307  38.226  1.00 30.41      A    C
ATOM   1102  CD1 ILE A 145      53.751 145.865  36.959  1.00 27.11      A    C
ATOM   1103  C   ILE A 145      52.627 149.460  40.355  1.00 33.93      A    C
ATOM   1104  O   ILE A 145      53.339 149.456  41.376  1.00 34.77      A    O
ATOM   1105  N   MET A 146      52.167 150.571  39.792  1.00 31.59      A    N
ATOM   1106  CA  MET A 146      52.467 151.870  40.353  1.00 32.81      A    C
ATOM   1107  CB  MET A 146      52.070 152.983  39.372  1.00 31.32      A    C
ATOM   1108  CG  MET A 146      52.903 152.970  38.079  1.00 32.99      A    C
ATOM   1109  SD  MET A 146      52.715 154.421  37.013  1.00 33.00      A    S
ATOM   1110  CE  MET A 146      51.066 154.125  36.278  1.00 31.04      A    C
ATOM   1111  C   MET A 146      51.715 152.010  41.675  1.00 33.04      A    C
ATOM   1112  O   MET A 146      52.235 152.572  42.644  1.00 33.23      A    O
ATOM   1113  N   ALA A 147      50.497 151.480  41.707  1.00 32.03      A    N
ATOM   1114  CA  ALA A 147      49.661 151.529  42.907  1.00 32.58      A    C
ATOM   1115  CB  ALA A 147      48.268 150.972  42.603  1.00 30.91      A    C
ATOM   1116  C   ALA A 147      50.318 150.700  44.000  1.00 31.25      A    C
ATOM   1117  O   ALA A 147      50.350 151.080  45.163  1.00 31.85      A    O
ATOM   1118  N   MET A 148      50.843 149.556  43.601  1.00 30.88      A    N
ATOM   1119  CA  MET A 148      51.503 148.667  44.520  1.00 29.14      A    C
ATOM   1120  CB  MET A 148      51.933 147.408  43.776  1.00 28.58      A    C
ATOM   1121  CG  MET A 148      52.660 146.429  44.623  1.00 26.39      A    C
ATOM   1122  SD  MET A 148      52.890 144.887  43.803  1.00 33.17      A    S
ATOM   1123  CE  MET A 148      54.175 145.351  42.561  1.00 22.10      A    C
ATOM   1124  C   MET A 148      52.708 149.363  45.143  1.00 31.23      A    C
ATOM   1125  O   MET A 148      52.936 149.254  46.346  1.00 30.34      A    O
ATOM   1126  N   ALA A 149      53.483 150.068  44.321  1.00 32.20      A    N
ATOM   1127  CA  ALA A 149      54.655 150.784  44.813  1.00 32.83      A    C
ATOM   1128  CB  ALA A 149      55.400 151.463  43.653  1.00 31.41      A    C
ATOM   1129  C   ALA A 149      54.194 151.831  45.824  1.00 32.18      A    C
ATOM   1130  O   ALA A 149      54.788 151.979  46.889  1.00 32.86      A    O
ATOM   1131  N   LEU A 150      53.136 152.559  45.491  1.00 30.54      A    N
ATOM   1132  CA  LEU A 150      52.634 153.572  46.401  1.00 31.42      A    C
ATOM   1133  CB  LEU A 150      51.502 154.368  45.746  1.00 32.59      A    C
ATOM   1134  CG  LEU A 150      51.933 155.358  44.667  1.00 30.95      A    C
ATOM   1135  CD1 LEU A 150      50.699 155.945  44.018  1.00 33.24      A    C
ATOM   1136  CD2 LEU A 150      52.762 156.458  45.270  1.00 27.68      A    C
ATOM   1137  C   LEU A 150      52.145 152.931  47.695  1.00 32.11      A    C
ATOM   1138  O   LEU A 150      52.450 153.407  48.793  1.00 32.52      A    O
ATOM   1139  N   ASP A 151      51.388 151.851  47.563  1.00 32.49      A    N
ATOM   1140  CA  ASP A 151      50.878 151.150  48.726  1.00 35.13      A    C
ATOM   1141  CB  ASP A 151      50.122 149.893  48.302  1.00 36.95      A    C
ATOM   1142  CG  ASP A 151      49.456 149.198  49.469  1.00 42.10      A    C
ATOM   1143  OD1 ASP A 151      49.126 149.885  50.465  1.00 42.02      A    O
ATOM   1144  OD2 ASP A 151      49.245 147.967  49.391  1.00 48.27      A    O
ATOM   1145  C   ASP A 151      52.047 150.791  49.634  1.00 33.63      A    C
ATOM   1146  O   ASP A 151      51.990 150.971  50.851  1.00 33.23      A    O
ATOM   1147  N   PHE A 152      53.116 150.305  49.021  1.00 32.31      A    N
ATOM   1148  CA  PHE A 152      54.327 149.936  49.738  1.00 30.67      A    C
ATOM   1149  CB  PHE A 152      55.388 149.493  48.735  1.00 28.32      A    C
ATOM   1150  CG  PHE A 152      56.761 149.389  49.319  1.00 27.77      A    C
ATOM   1151  CD1 PHE A 152      57.072 148.379  50.217  1.00 23.66      A    C
ATOM   1152  CD2 PHE A 152      57.746 150.302  48.973  1.00 26.36      A    C
ATOM   1153  CE1 PHE A 152      58.350 148.269  50.763  1.00 26.49      A    C
ATOM   1154  CE2 PHE A 152      59.039 150.196  49.524  1.00 28.84      A    C
ATOM   1155  CZ  PHE A 152      59.330 149.170  50.419  1.00 24.40      A    C
ATOM   1156  C   PHE A 152      54.861 151.096  50.588  1.00 30.66      A    C
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FIGURE 11-29

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ATOM   1157  O   PHE A 152      55.152 150.934  51.776  1.00 31.64      A    O
ATOM   1158  N   PHE A 153      54.996 152.269  49.988  1.00 30.08      A    N
ATOM   1159  CA  PHE A 153      55.484 153.406  50.739  1.00 32.71      A    C
ATOM   1160  CB  PHE A 153      55.776 154.588  49.805  1.00 32.98      A    C
ATOM   1161  CG  PHE A 153      57.046 154.418  49.025  1.00 35.69      A    C
ATOM   1162  CD1 PHE A 153      57.017 154.171  47.651  1.00 32.99      A    C
ATOM   1163  CD2 PHE A 153      58.281 154.422  49.683  1.00 37.04      A    C
ATOM   1164  CE1 PHE A 153      58.192 153.927  46.947  1.00 33.75      A    C
ATOM   1165  CE2 PHE A 153      59.471 154.177  48.980  1.00 36.45      A    C
ATOM   1166  CZ  PHE A 153      59.423 153.928  47.610  1.00 36.03      A    C
ATOM   1167  C   PHE A 153      54.518 153.803  51.851  1.00 33.43      A    C
ATOM   1168  O   PHE A 153      54.952 154.134  52.954  1.00 32.37      A    O
ATOM   1169  N   LYS A 154      53.218 153.769  51.558  1.00 32.94      A    N
ATOM   1170  CA  LYS A 154      52.206 154.094  52.546  1.00 31.38      A    C
ATOM   1171  CB  LYS A 154      50.808 153.943  51.951  1.00 34.21      A    C
ATOM   1172  CG  LYS A 154      49.705 153.852  52.992  1.00 34.61      A    C
ATOM   1173  CD  LYS A 154      48.337 153.650  52.380  1.00 38.25      A    C
ATOM   1174  CE  LYS A 154      47.290 153.484  53.491  1.00 45.50      A    C
ATOM   1175  NZ  LYS A 154      45.866 153.503  53.001  1.00 48.22      A    N
ATOM   1176  C   LYS A 154      52.353 153.134  53.725  1.00 33.69      A    C
ATOM   1177  O   LYS A 154      52.191 153.518  54.880  1.00 33.00      A    O
ATOM   1178  N   GLN A 155      52.667 151.879  53.433  1.00 35.21      A    N
ATOM   1179  CA  GLN A 155      52.836 150.899  54.497  1.00 37.24      A    C
ATOM   1180  CB  GLN A 155      52.961 149.499  53.909  1.00 38.04      A    C
ATOM   1181  CG  GLN A 155      51.632 148.932  53.493  1.00 44.85      A    C
ATOM   1182  CD  GLN A 155      50.666 148.837  54.663  1.00 46.82      A    C
ATOM   1183  OE1 GLN A 155      50.943 148.152  55.661  1.00 47.10      A    O
ATOM   1184  NE2 GLN A 155      49.533 149.531  54.556  1.00 44.03      A    N
ATOM   1185  C   GLN A 155      54.045 151.209  55.375  1.00 36.29      A    C
ATOM   1186  O   GLN A 155      54.008 150.995  56.577  1.00 34.83      A    O
ATOM   1187  N   LEU A 156      55.121 151.700  54.771  1.00 34.74      A    N
ATOM   1188  CA  LEU A 156      56.305 152.055  55.543  1.00 34.06      A    C
ATOM   1189  CB  LEU A 156      57.484 152.372  54.615  1.00 31.88      A    C
ATOM   1190  CG  LEU A 156      58.095 151.222  53.821  1.00 31.16      A    C
ATOM   1191  CD1 LEU A 156      59.167 151.775  52.905  1.00 32.62      A    C
ATOM   1192  CD2 LEU A 156      58.668 150.173  54.765  1.00 29.85      A    C
ATOM   1193  C   LEU A 156      56.020 153.293  56.396  1.00 34.46      A    C
ATOM   1194  O   LEU A 156      56.710 153.550  57.380  1.00 35.82      A    O
ATOM   1195  N   GLY A 157      55.008 154.067  56.012  1.00 33.47      A    N
ATOM   1196  CA  GLY A 157      54.704 155.284  56.745  1.00 30.20      A    C
ATOM   1197  C   GLY A 157      55.289 156.504  56.044  1.00 29.38      A    C
ATOM   1198  O   GLY A 157      55.316 157.604  56.598  1.00 29.55      A    O
ATOM   1199  N   ILE A 158      55.793 156.304  54.830  1.00 27.38      A    N
ATOM   1200  CA  ILE A 158      56.336 157.403  54.048  1.00 26.39      A    C
ATOM   1201  CB  ILE A 158      57.320 156.895  52.966  1.00 25.42      A    C
ATOM   1202  CG2 ILE A 158      57.466 157.937  51.857  1.00 22.99      A    C
ATOM   1203  CG1 ILE A 158      58.674 156.603  53.621  1.00 24.95      A    C
ATOM   1204  CD1 ILE A 158      59.685 155.883  52.739  1.00 26.67      A    C
ATOM   1205  C   ILE A 158      55.136 158.089  53.404  1.00 27.66      A    C
ATOM   1206  O   ILE A 158      54.382 157.472  52.654  1.00 29.05      A    O
ATOM   1207  N   GLN A 159      54.968 159.375  53.685  1.00 28.74      A    N
ATOM   1208  CA  GLN A 159      53.816 160.107  53.182  1.00 30.27      A    C
ATOM   1209  CB  GLN A 159      53.023 160.663  54.362  1.00 28.91      A    C
ATOM   1210  CG  GLN A 159      52.430 159.623  55.260  1.00 34.53      A    C
ATOM   1211  CD  GLN A 159      51.793 160.245  56.490  1.00 37.37      A    C
ATOM   1212  OE1 GLN A 159      52.459 160.458  57.501  1.00 39.94      A    O
ATOM   1213  NE2 GLN A 159      50.505 160.557  56.401  1.00 36.40      A    N
ATOM   1214  C   GLN A 159      54.073 161.257  52.240  1.00 30.30      A    C
ATOM   1215  O   GLN A 159      53.185 161.644  51.481  1.00 29.64      A    O
ATOM   1216  N   GLN A 160      55.269 161.822  52.314  1.00 31.28      A    N
ATOM   1217  CA  GLN A 160      55.597 162.978  51.512  1.00 32.31      A    C
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FIGURE 11-30

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ATOM   1218  CB  GLN A 160      56.525 163.875  52.326  1.00 33.53      A    C
ATOM   1219  CG  GLN A 160      55.986 164.075  53.737  1.00 32.45      A    C
ATOM   1220  CD  GLN A 160      56.732 165.125  54.529  1.00 33.07      A    C
ATOM   1221  OE1 GLN A 160      56.122 165.940  55.226  1.00 35.11      A    O
ATOM   1222  NE2 GLN A 160      58.049 165.110  54.436  1.00 32.01      A    N
ATOM   1223  C   GLN A 160      56.205 162.573  50.192  1.00 33.14      A    C
ATOM   1224  O   GLN A 160      57.400 162.765  49.945  1.00 34.05      A    O
ATOM   1225  N   ILE A 161      55.359 162.007  49.342  1.00 32.33      A    N
ATOM   1226  CA  ILE A 161      55.792 161.538  48.037  1.00 32.66      A    C
ATOM   1227  CB  ILE A 161      55.906 160.016  48.007  1.00 32.02      A    C
ATOM   1228  CG2 ILE A 161      57.135 159.561  48.776  1.00 31.37      A    C
ATOM   1229  CG1 ILE A 161      54.635 159.402  48.583  1.00 27.90      A    C
ATOM   1230  CD1 ILE A 161      54.569 157.894  48.449  1.00 27.21      A    C
ATOM   1231  C   ILE A 161      54.806 161.929  46.961  1.00 33.67      A    C
ATOM   1232  O   ILE A 161      53.681 162.341  47.249  1.00 35.12      A    O
ATOM   1233  N   LYS A 162      55.238 161.807  45.716  1.00 33.45      A    N
ATOM   1234  CA  LYS A 162      54.369 162.104  44.595  1.00 34.46      A    C
ATOM   1235  CB  LYS A 162      54.499 163.563  44.145  1.00 36.42      A    C
ATOM   1236  CG  LYS A 162      55.832 163.950  43.509  1.00 40.98      A    C
ATOM   1237  CD  LYS A 162      55.728 165.346  42.896  1.00 40.55      A    C
ATOM   1238  CE  LYS A 162      57.052 165.827  42.305  1.00 42.40      A    C
ATOM   1239  NZ  LYS A 162      56.890 167.165  41.654  1.00 41.41      A    N
ATOM   1240  C   LYS A 162      54.696 161.172  43.456  1.00 33.57      A    C
ATOM   1241  O   LYS A 162      55.855 160.808  43.251  1.00 32.42      A    O
ATOM   1242  N   LEU A 163      53.661 160.753  42.741  1.00 33.53      A    N
ATOM   1243  CA  LEU A 163      53.849 159.874  41.604  1.00 32.52      A    C
ATOM   1244  CB  LEU A 163      52.652 158.942  41.459  1.00 32.31      A    C
ATOM   1245  CG  LEU A 163      52.566 158.140  40.151  1.00 36.33      A    C
ATOM   1246  CD1 LEU A 163      53.720 157.142  40.020  1.00 32.38      A    C
ATOM   1247  CD2 LEU A 163      51.229 157.412  40.140  1.00 37.64      A    C
ATOM   1248  C   LEU A 163      53.985 160.767  40.375  1.00 31.88      A    C
ATOM   1249  O   LEU A 163      53.175 161.660  40.157  1.00 34.87      A    O
ATOM   1250  N   VAL A 164      55.033 160.550  39.595  1.00 30.20      A    N
ATOM   1251  CA  VAL A 164      55.263 161.336  38.396  1.00 30.60      A    C
ATOM   1252  CB  VAL A 164      56.571 162.169  38.507  1.00 34.19      A    C
ATOM   1253  CG1 VAL A 164      56.764 163.040  37.245  1.00 32.04      A    C
ATOM   1254  CG2 VAL A 164      56.501 163.066  39.742  1.00 31.56      A    C
ATOM   1255  C   VAL A 164      55.340 160.352  37.229  1.00 30.97      A    C
ATOM   1256  O   VAL A 164      56.089 159.375  37.264  1.00 29.64      A    O
ATOM   1257  N   ILE A 165      54.532 160.599  36.207  1.00 31.59      A    N
ATOM   1258  CA  ILE A 165      54.484 159.706  35.065  1.00 34.30      A    C
ATOM   1259  CB  ILE A 165      53.127 159.032  34.956  1.00 36.33      A    C
ATOM   1260  CG2 ILE A 165      52.755 158.371  36.283  1.00 35.78      A    C
ATOM   1261  CG1 ILE A 165      52.083 160.092  34.568  1.00 33.29      A    C
ATOM   1262  CD1 ILE A 165      50.690 159.562  34.484  1.00 34.28      A    C
ATOM   1263  C   ILE A 165      54.698 160.440  33.760  1.00 35.50      A    C
ATOM   1264  O   ILE A 165      54.734 161.665  33.698  1.00 36.61      A    O
ATOM   1265  N   ASN A 166      54.815 159.658  32.704  1.00 37.34      A    N
ATOM   1266  CA  ASN A 166      55.009 160.192  31.381  1.00 37.67      A    C
ATOM   1267  CB  ASN A 166      56.373 160.887  31.295  1.00 36.94      A    C
ATOM   1268  CG  ASN A 166      56.595 161.581  29.964  1.00 36.96      A    C
ATOM   1269  OD1 ASN A 166      55.652 162.055  29.331  1.00 34.31      A    O
ATOM   1270  ND2 ASN A 166      57.852 161.665  29.546  1.00 35.87      A    N
ATOM   1271  C   ASN A 166      54.953 158.978  30.487  1.00 37.58      A    C
ATOM   1272  O   ASN A 166      54.814 157.860  30.969  1.00 37.93      A    O
ATOM   1273  N   SER A 167      55.019 159.191  29.185  1.00 39.30      A    N
ATOM   1274  CA  SER A 167      55.013 158.065  28.260  1.00 38.39      A    C
ATOM   1275  CB  SER A 167      53.649 157.899  27.599  1.00 38.99      A    C
ATOM   1276  OG  SER A 167      53.711 156.868  26.633  1.00 39.29      A    O
ATOM   1277  C   SER A 167      56.040 158.344  27.194  1.00 37.79      A    C
ATOM   1278  O   SER A 167      56.216 159.497  26.782  1.00 36.28      A    O
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FIGURE 11-31

ATOM	1279	N	LEU	A	168	56.735	157.297	26.772	1.00	37.62	A	N
ATOM	1280	CA	LEU	A	168	57.732	157.425	25.717	1.00	39.84	A	C
ATOM	1281	CB	LEU	A	168	59.033	156.697	26.097	1.00	35.67	A	C
ATOM	1282	CG	LEU	A	168	59.781	157.193	27.346	1.00	34.08	A	C
ATOM	1283	CD1	LEU	A	168	61.045	156.380	27.540	1.00	33.90	A	C
ATOM	1284	CD2	LEU	A	168	60.117	158.678	27.215	1.00	33.62	A	C
ATOM	1285	C	LEU	A	168	57.114	156.781	24.475	1.00	42.42	A	C
ATOM	1286	O	LEU	A	168	57.754	156.682	23.427	1.00	44.26	A	O
ATOM	1287	N	GLY	A	169	55.864	156.340	24.612	1.00	41.14	A	N
ATOM	1288	CA	GLY	A	169	55.175	155.698	23.510	1.00	42.48	A	C
ATOM	1289	C	GLY	A	169	55.996	154.619	22.830	1.00	44.24	A	C
ATOM	1290	O	GLY	A	169	56.981	154.129	23.381	1.00	43.91	A	O
ATOM	1291	N	ASP	A	170	55.586	154.253	21.621	1.00	46.17	A	N
ATOM	1292	CA	ASP	A	170	56.267	153.225	20.825	1.00	46.45	A	C
ATOM	1293	CB	ASP	A	170	55.245	152.490	19.979	1.00	46.77	A	C
ATOM	1294	CG	ASP	A	170	54.481	153.429	19.075	1.00	45.14	A	C
ATOM	1295	OD1	ASP	A	170	53.476	153.000	18.476	1.00	45.00	A	O
ATOM	1296	OD2	ASP	A	170	54.895	154.605	18.967	1.00	44.44	A	O
ATOM	1297	C	ASP	A	170	57.314	153.835	19.895	1.00	47.01	A	C
ATOM	1298	O	ASP	A	170	57.510	155.050	19.869	1.00	48.40	A	O
ATOM	1299	N	LYS	A	171	57.957	152.980	19.110	1.00	48.99	A	N
ATOM	1300	CA	LYS	A	171	58.999	153.401	18.180	1.00	50.42	A	C
ATOM	1301	CB	LYS	A	171	59.538	152.187	17.427	1.00	52.12	A	C
ATOM	1302	CG	LYS	A	171	60.145	151.140	18.342	1.00	57.59	A	C
ATOM	1303	CD	LYS	A	171	60.545	149.872	17.589	1.00	61.15	A	C
ATOM	1304	CE	LYS	A	171	60.986	148.774	18.555	1.00	63.24	A	C
ATOM	1305	NZ	LYS	A	171	61.007	147.415	17.917	1.00	66.27	A	N
ATOM	1306	C	LYS	A	171	58.537	154.464	17.192	1.00	50.48	A	C
ATOM	1307	O	LYS	A	171	59.235	155.454	16.974	1.00	51.02	A	O
ATOM	1308	N	GLU	A	172	57.370	154.267	16.588	1.00	50.86	A	N
ATOM	1309	CA	GLU	A	172	56.863	155.255	15.643	1.00	51.65	A	C
ATOM	1310	CB	GLU	A	172	55.447	154.898	15.177	1.00	52.10	A	C
ATOM	1311	CG	GLU	A	172	55.001	155.698	13.958	1.00	54.57	A	C
ATOM	1312	CD	GLU	A	172	53.491	155.797	13.812	1.00	56.80	A	C
ATOM	1313	OE1	GLU	A	172	52.795	154.759	13.875	1.00	56.07	A	O
ATOM	1314	OE2	GLU	A	172	52.998	156.930	13.620	1.00	60.34	A	O
ATOM	1315	C	GLU	A	172	56.833	156.606	16.357	1.00	51.82	A	C
ATOM	1316	O	GLU	A	172	57.407	157.591	15.885	1.00	51.40	A	O
ATOM	1317	N	THR	A	173	56.168	156.633	17.509	1.00	51.04	A	N
ATOM	1318	CA	THR	A	173	56.051	157.847	18.305	1.00	50.99	A	C
ATOM	1319	CB	THR	A	173	55.284	157.572	19.627	1.00	51.51	A	C
ATOM	1320	OG1	THR	A	173	54.007	156.996	19.327	1.00	50.92	A	O
ATOM	1321	CG2	THR	A	173	55.071	158.872	20.412	1.00	50.07	A	C
ATOM	1322	C	THR	A	173	57.427	158.419	18.641	1.00	49.04	A	C
ATOM	1323	O	THR	A	173	57.656	159.623	18.532	1.00	48.57	A	O
ATOM	1324	N	ARG	A	174	58.345	157.558	19.057	1.00	49.30	A	N
ATOM	1325	CA	ARG	A	174	59.679	158.027	19.402	1.00	51.87	A	C
ATOM	1326	CB	ARG	A	174	60.561	156.864	19.856	1.00	52.86	A	C
ATOM	1327	CG	ARG	A	174	60.199	156.320	21.220	1.00	57.33	A	C
ATOM	1328	CD	ARG	A	174	60.537	157.289	22.356	1.00	58.58	A	C
ATOM	1329	NE	ARG	A	174	61.645	156.780	23.161	1.00	62.63	A	N
ATOM	1330	CZ	ARG	A	174	62.921	157.057	22.929	1.00	63.19	A	C
ATOM	1331	NH1	ARG	A	174	63.862	156.544	23.705	1.00	63.36	A	N
ATOM	1332	NH2	ARG	A	174	63.253	157.871	21.936	1.00	65.21	A	N
ATOM	1333	C	ARG	A	174	60.328	158.721	18.219	1.00	52.53	A	C
ATOM	1334	O	ARG	A	174	60.758	159.867	18.323	1.00	52.94	A	O
ATOM	1335	N	ALA	A	175	60.384	158.021	17.091	1.00	53.69	A	N
ATOM	1336	CA	ALA	A	175	60.996	158.554	15.880	1.00	53.92	A	C
ATOM	1337	CB	ALA	A	175	60.765	157.596	14.717	1.00	54.66	A	C
ATOM	1338	C	ALA	A	175	60.509	159.954	15.508	1.00	53.43	A	C
ATOM	1339	O	ALA	A	175	61.317	160.871	15.360	1.00	54.44	A	O

FIGURE 11-32

```
ATOM   1340  N   THR A 176      59.199 160.134  15.374  1.00 51.87      A    N
ATOM   1341  CA  THR A 176      58.694 161.444  14.990  1.00 52.04      A    C
ATOM   1342  CB  THR A 176      57.186 161.384  14.561  1.00 52.16      A    C
ATOM   1343  OG1 THR A 176      56.486 162.517  15.085  1.00 53.49      A    O
ATOM   1344  CG2 THR A 176      56.531 160.107  15.014  1.00 51.86      A    C
ATOM   1345  C   THR A 176      58.924 162.561  16.011  1.00 53.24      A    C
ATOM   1346  O   THR A 176      59.376 163.648  15.639  1.00 54.52      A    O
ATOM   1347  N   TYR A 177      58.640 162.313  17.289  1.00 53.33      A    N
ATOM   1348  CA  TYR A 177      58.856 163.345  18.301  1.00 51.35      A    C
ATOM   1349  CB  TYR A 177      58.357 162.889  19.679  1.00 52.46      A    C
ATOM   1350  CG  TYR A 177      58.803 163.804  20.804  1.00 49.40      A    C
ATOM   1351  CD1 TYR A 177      59.888 163.470  21.617  1.00 47.60      A    C
ATOM   1352  CE1 TYR A 177      60.343 164.342  22.607  1.00 45.86      A    C
ATOM   1353  CD2 TYR A 177      58.180 165.037  21.012  1.00 49.80      A    C
ATOM   1354  CE2 TYR A 177      58.627 165.914  21.995  1.00 46.66      A    C
ATOM   1355  CZ  TYR A 177      59.706 165.561  22.788  1.00 47.09      A    C
ATOM   1356  OH  TYR A 177      60.134 166.431  23.765  1.00 46.11      A    O
ATOM   1357  C   TYR A 177      60.335 163.695  18.391  1.00 51.57      A    C
ATOM   1358  O   TYR A 177      60.694 164.820  18.737  1.00 50.54      A    O
ATOM   1359  N   ARG A 178      61.186 162.723  18.077  1.00 51.08      A    N
ATOM   1360  CA  ARG A 178      62.630 162.926  18.110  1.00 52.40      A    C
ATOM   1361  CB  ARG A 178      63.357 161.629  17.754  1.00 53.46      A    C
ATOM   1362  CG  ARG A 178      64.870 161.762  17.765  1.00 57.58      A    C
ATOM   1363  CD  ARG A 178      65.554 160.404  17.736  1.00 61.79      A    C
ATOM   1364  NE  ARG A 178      66.971 160.516  18.071  1.00 66.28      A    N
ATOM   1365  CZ  ARG A 178      67.711 159.512  18.533  1.00 69.02      A    C
ATOM   1366  NH1 ARG A 178      67.168 158.309  18.716  1.00 69.30      A    N
ATOM   1367  NH2 ARG A 178      68.990 159.712  18.831  1.00 69.14      A    N
ATOM   1368  C   ARG A 178      63.032 164.008  17.117  1.00 52.84      A    C
ATOM   1369  O   ARG A 178      63.868 164.869  17.406  1.00 51.08      A    O
ATOM   1370  N   GLN A 179      62.433 163.942  15.936  1.00 53.43      A    N
ATOM   1371  CA  GLN A 179      62.710 164.901  14.885  1.00 52.97      A    C
ATOM   1372  CB  GLN A 179      62.054 164.447  13.577  1.00 52.43      A    C
ATOM   1373  CG  GLN A 179      62.392 165.316  12.393  1.00 51.30      A    C
ATOM   1374  CD  GLN A 179      63.884 165.470  12.223  1.00 51.23      A    C
ATOM   1375  OE1 GLN A 179      64.597 164.488  12.032  1.00 51.82      A    O
ATOM   1376  NE2 GLN A 179      64.369 166.708  12.303  1.00 51.43      A    N
ATOM   1377  C   GLN A 179      62.161 166.259  15.303  1.00 52.46      A    C
ATOM   1378  O   GLN A 179      62.828 167.284  15.153  1.00 54.49      A    O
ATOM   1379  N   ALA A 180      60.948 166.260  15.841  1.00 50.64      A    N
ATOM   1380  CA  ALA A 180      60.316 167.502  16.270  1.00 50.84      A    C
ATOM   1381  CB  ALA A 180      58.897 167.227  16.767  1.00 50.91      A    C
ATOM   1382  C   ALA A 180      61.116 168.226  17.349  1.00 51.61      A    C
ATOM   1383  O   ALA A 180      61.165 169.457  17.368  1.00 52.56      A    O
ATOM   1384  N   LEU A 181      61.739 167.467  18.247  1.00 50.92      A    N
ATOM   1385  CA  LEU A 181      62.524 168.069  19.316  1.00 51.75      A    C
ATOM   1386  CB  LEU A 181      62.880 167.032  20.388  1.00 49.45      A    C
ATOM   1387  CG  LEU A 181      63.688 167.623  21.554  1.00 48.43      A    C
ATOM   1388  CD1 LEU A 181      62.874 168.727  22.187  1.00 47.38      A    C
ATOM   1389  CD2 LEU A 181      64.031 166.555  22.588  1.00 47.88      A    C
ATOM   1390  C   LEU A 181      63.802 168.681  18.763  1.00 52.72      A    C
ATOM   1391  O   LEU A 181      64.233 169.753  19.193  1.00 54.09      A    O
ATOM   1392  N   ILE A 182      64.413 167.986  17.812  1.00 54.25      A    N
ATOM   1393  CA  ILE A 182      65.642 168.465  17.195  1.00 54.71      A    C
ATOM   1394  CB  ILE A 182      66.211 167.417  16.208  1.00 55.92      A    C
ATOM   1395  CG2 ILE A 182      67.304 168.043  15.343  1.00 56.07      A    C
ATOM   1396  CG1 ILE A 182      66.748 166.217  16.997  1.00 56.55      A    C
ATOM   1397  CD1 ILE A 182      67.275 165.078  16.138  1.00 55.80      A    C
ATOM   1398  C   ILE A 182      65.361 169.766  16.451  1.00 53.56      A    C
ATOM   1399  O   ILE A 182      66.140 170.712  16.525  1.00 53.27      A    O
ATOM   1400  N   ASP A 183      64.228 169.820  15.763  1.00 52.40      A    N
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FIGURE 11-33

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ATOM   1401  CA  ASP A 183      63.876 171.009  15.009  1.00 52.80      A    C
ATOM   1402  CB  ASP A 183      62.610 170.770  14.178  1.00 54.03      A    C
ATOM   1403  CG  ASP A 183      62.800 169.692  13.118  1.00 56.84      A    C
ATOM   1404  OD1 ASP A 183      63.959 169.416  12.726  1.00 57.64      A    O
ATOM   1405  OD2 ASP A 183      61.787 169.124  12.662  1.00 60.40      A    O
ATOM   1406  C   ASP A 183      63.668 172.179  15.943  1.00 52.54      A    C
ATOM   1407  O   ASP A 183      63.783 173.344  15.543  1.00 53.22      A    O
ATOM   1408  N   TYR A 184      63.369 171.867  17.198  1.00 51.51      A    N
ATOM   1409  CA  TYR A 184      63.142 172.903  18.191  1.00 48.41      A    C
ATOM   1410  CB  TYR A 184      62.227 172.400  19.305  1.00 44.87      A    C
ATOM   1411  CG  TYR A 184      62.149 173.386  20.443  1.00 41.57      A    C
ATOM   1412  CD1 TYR A 184      61.368 174.536  20.333  1.00 40.44      A    C
ATOM   1413  CE1 TYR A 184      61.360 175.498  21.322  1.00 38.24      A    C
ATOM   1414  CD2 TYR A 184      62.925 173.221  21.590  1.00 38.58      A    C
ATOM   1415  CE2 TYR A 184      62.931 174.188  22.593  1.00 41.00      A    C
ATOM   1416  CZ  TYR A 184      62.150 175.323  22.447  1.00 40.73      A    C
ATOM   1417  OH  TYR A 184      62.195 176.320  23.389  1.00 41.24      A    O
ATOM   1418  C   TYR A 184      64.439 173.365  18.829  1.00 49.05      A    C
ATOM   1419  O   TYR A 184      64.641 174.561  19.055  1.00 49.65      A    O
ATOM   1420  N   LEU A 185      65.309 172.407  19.126  1.00 48.90      A    N
ATOM   1421  CA  LEU A 185      66.568 172.695  19.792  1.00 50.06      A    C
ATOM   1422  CB  LEU A 185      67.101 171.417  20.445  1.00 48.21      A    C
ATOM   1423  CG  LEU A 185      66.230 170.793  21.541  1.00 48.38      A    C
ATOM   1424  CD1 LEU A 185      66.935 169.571  22.106  1.00 49.26      A    C
ATOM   1425  CD2 LEU A 185      65.966 171.802  22.643  1.00 47.76      A    C
ATOM   1426  C   LEU A 185      67.666 173.328  18.939  1.00 52.03      A    C
ATOM   1427  O   LEU A 185      68.445 174.143  19.441  1.00 50.64      A    O
ATOM   1428  N   GLU A 186      67.740 172.953  17.663  1.00 52.41      A    N
ATOM   1429  CA  GLU A 186      68.772 173.495  16.781  1.00 54.08      A    C
ATOM   1430  CB  GLU A 186      68.587 172.962  15.356  1.00 56.46      A    C
ATOM   1431  CG  GLU A 186      68.700 171.442  15.279  1.00 59.41      A    C
ATOM   1432  CD  GLU A 186      68.698 170.911  13.854  1.00 63.02      A    C
ATOM   1433  OE1 GLU A 186      67.784 171.278  13.080  1.00 64.23      A    O
ATOM   1434  OE2 GLU A 186      69.608 170.117  13.514  1.00 63.42      A    O
ATOM   1435  C   GLU A 186      68.847 175.022  16.787  1.00 52.51      A    C
ATOM   1436  O   GLU A 186      69.925 175.582  16.953  1.00 52.71      A    O
ATOM   1437  N   PRO A 187      67.704 175.715  16.621  1.00 52.68      A    N
ATOM   1438  CD  PRO A 187      66.370 175.166  16.313  1.00 51.51      A    C
ATOM   1439  CA  PRO A 187      67.670 177.185  16.620  1.00 52.06      A    C
ATOM   1440  CB  PRO A 187      66.188 177.498  16.429  1.00 50.81      A    C
ATOM   1441  CG  PRO A 187      65.692 176.331  15.651  1.00 51.27      A    C
ATOM   1442  C   PRO A 187      68.203 177.800  17.923  1.00 53.64      A    C
ATOM   1443  O   PRO A 187      68.436 179.015  18.001  1.00 53.73      A    O
ATOM   1444  N   HIS A 188      68.373 176.961  18.944  1.00 52.99      A    N
ATOM   1445  CA  HIS A 188      68.865 177.405  20.245  1.00 52.32      A    C
ATOM   1446  CB  HIS A 188      67.809 177.161  21.326  1.00 49.17      A    C
ATOM   1447  CG  HIS A 188      66.509 177.857  21.081  1.00 47.19      A    C
ATOM   1448  CD2 HIS A 188      65.315 177.387  20.646  1.00 47.52      A    C
ATOM   1449  ND1 HIS A 188      66.331 179.205  21.304  1.00 45.21      A    N
ATOM   1450  CE1 HIS A 188      65.085 179.535  21.020  1.00 46.24      A    C
ATOM   1451  NE2 HIS A 188      64.446 178.450  20.620  1.00 46.81      A    N
ATOM   1452  C   HIS A 188      70.123 176.640  20.625  1.00 54.46      A    C
ATOM   1453  O   HIS A 188      70.649 176.801  21.727  1.00 55.71      A    O
ATOM   1454  N   MET A 189      70.600 175.801  19.717  1.00 55.99      A    N
ATOM   1455  CA  MET A 189      71.778 174.991  19.981  1.00 59.25      A    C
ATOM   1456  CB  MET A 189      72.287 174.386  18.674  1.00 62.05      A    C
ATOM   1457  CG  MET A 189      73.556 173.559  18.804  1.00 63.37      A    C
ATOM   1458  SD  MET A 189      73.807 172.476  17.362  1.00 67.91      A    S
ATOM   1459  CE  MET A 189      72.797 173.324  16.082  1.00 64.89      A    C
ATOM   1460  C   MET A 189      72.908 175.724  20.690  1.00 61.05      A    C
ATOM   1461  O   MET A 189      73.450 175.225  21.675  1.00 62.20      A    O
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FIGURE 11-34

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ATOM   1462  N   ALA A 190      73.259 176.909  20.205  1.00 62.44      A    N
ATOM   1463  CA  ALA A 190      74.349 177.671  20.805  1.00 64.54      A    C
ATOM   1464  CB  ALA A 190      74.566 178.962  20.030  1.00 65.44      A    C
ATOM   1465  C   ALA A 190      74.150 177.982  22.289  1.00 65.85      A    C
ATOM   1466  O   ALA A 190      75.119 178.083  23.043  1.00 65.06      A    O
ATOM   1467  N   GLU A 191      72.899 178.124  22.715  1.00 67.77      A    N
ATOM   1468  CA  GLU A 191      72.630 178.442  24.112  1.00 68.10      A    C
ATOM   1469  CB  GLU A 191      71.348 179.271  24.233  1.00 70.80      A    C
ATOM   1470  CG  GLU A 191      71.513 180.467  25.156  1.00 73.51      A    C
ATOM   1471  CD  GLU A 191      72.396 181.544  24.548  1.00 75.01      A    C
ATOM   1472  OE1 GLU A 191      73.146 182.199  25.304  1.00 75.81      A    O
ATOM   1473  OE2 GLU A 191      72.331 181.742  23.313  1.00 74.87      A    O
ATOM   1474  C   GLU A 191      72.538 177.216  25.018  1.00 67.23      A    C
ATOM   1475  O   GLU A 191      72.450 177.350  26.242  1.00 66.99      A    O
ATOM   1476  N   LEU A 192      72.559 176.025  24.428  1.00 64.91      A    N
ATOM   1477  CA  LEU A 192      72.492 174.805  25.224  1.00 63.18      A    C
ATOM   1478  CB  LEU A 192      72.193 173.597  24.338  1.00 58.38      A    C
ATOM   1479  CG  LEU A 192      70.776 173.537  23.773  1.00 55.72      A    C
ATOM   1480  CD1 LEU A 192      70.619 172.285  22.933  1.00 55.73      A    C
ATOM   1481  CD2 LEU A 192      69.761 173.542  24.916  1.00 54.99      A    C
ATOM   1482  C   LEU A 192      73.798 174.584  25.974  1.00 64.46      A    C
ATOM   1483  O   LEU A 192      74.862 175.010  25.527  1.00 64.15      A    O
ATOM   1484  N   SER A 193      73.707 173.919  27.121  1.00 66.04      A    N
ATOM   1485  CA  SER A 193      74.875 173.633  27.946  1.00 67.12      A    C
ATOM   1486  CB  SER A 193      74.457 172.869  29.196  1.00 66.76      A    C
ATOM   1487  OG  SER A 193      74.029 171.564  28.854  1.00 65.80      A    O
ATOM   1488  C   SER A 193      75.894 172.798  27.184  1.00 68.44      A    C
ATOM   1489  O   SER A 193      75.621 172.327  26.079  1.00 68.75      A    O
ATOM   1490  N   GLU A 194      77.066 172.614  27.784  1.00 69.72      A    N
ATOM   1491  CA  GLU A 194      78.121 171.823  27.168  1.00 72.05      A    C
ATOM   1492  CB  GLU A 194      79.310 171.652  28.125  1.00 75.45      A    C
ATOM   1493  CG  GLU A 194      80.474 172.623  27.915  1.00 78.77      A    C
ATOM   1494  CD  GLU A 194      81.752 172.172  28.630  1.00 81.32      A    C
ATOM   1495  OE1 GLU A 194      82.778 172.886  28.536  1.00 82.30      A    O
ATOM   1496  OE2 GLU A 194      81.733 171.102  29.283  1.00 80.61      A    O
ATOM   1497  C   GLU A 194      77.573 170.451  26.826  1.00 71.74      A    C
ATOM   1498  O   GLU A 194      77.426 170.094  25.659  1.00 70.79      A    O
ATOM   1499  N   ASP A 195      77.269 169.683  27.864  1.00 72.77      A    N
ATOM   1500  CA  ASP A 195      76.745 168.343  27.682  1.00 73.51      A    C
ATOM   1501  CB  ASP A 195      76.357 167.751  29.035  1.00 76.66      A    C
ATOM   1502  CG  ASP A 195      77.066 166.444  29.316  1.00 79.14      A    C
ATOM   1503  OD1 ASP A 195      76.947 165.517  28.482  1.00 80.54      A    O
ATOM   1504  OD2 ASP A 195      77.741 166.343  30.365  1.00 79.76      A    O
ATOM   1505  C   ASP A 195      75.545 168.318  26.741  1.00 72.26      A    C
ATOM   1506  O   ASP A 195      75.526 167.558  25.771  1.00 71.25      A    O
ATOM   1507  N   SER A 196      74.551 169.156  27.027  1.00 70.82      A    N
ATOM   1508  CA  SER A 196      73.344 169.221  26.209  1.00 70.41      A    C
ATOM   1509  CB  SER A 196      72.424 170.335  26.710  1.00 70.66      A    C
ATOM   1510  OG  SER A 196      71.955 170.060  28.019  1.00 70.01      A    O
ATOM   1511  C   SER A 196      73.611 169.412  24.719  1.00 70.65      A    C
ATOM   1512  O   SER A 196      72.902 168.851  23.888  1.00 70.46      A    O
ATOM   1513  N   GLN A 197      74.626 170.200  24.375  1.00 71.88      A    N
ATOM   1514  CA  GLN A 197      74.956 170.431  22.966  1.00 73.00      A    C
ATOM   1515  CB  GLN A 197      75.953 171.585  22.821  1.00 72.13      A    C
ATOM   1516  CG  GLN A 197      75.282 172.943  22.701  1.00 71.86      A    C
ATOM   1517  CD  GLN A 197      76.269 174.070  22.511  1.00 71.16      A    C
ATOM   1518  OE1 GLN A 197      77.036 174.396  23.412  1.00 69.32      A    O
ATOM   1519  NE2 GLN A 197      76.257 174.672  21.330  1.00 72.65      A    N
ATOM   1520  C   GLN A 197      75.508 169.197  22.266  1.00 73.69      A    C
ATOM   1521  O   GLN A 197      75.240 168.977  21.085  1.00 72.86      A    O
ATOM   1522  N   ARG A 198      76.281 168.395  22.991  1.00 76.26      A    N
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FIGURE 11-35

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ATOM   1523  CA  ARG A 198      76.852 167.184  22.416  1.00 78.78      A    C
ATOM   1524  CB  ARG A 198      77.997 166.657  23.287  1.00 80.50      A    C
ATOM   1525  CG  ARG A 198      79.161 167.628  23.409  1.00 83.85      A    C
ATOM   1526  CD  ARG A 198      80.441 166.944  23.868  1.00 85.69      A    C
ATOM   1527  NE  ARG A 198      81.554 167.891  23.932  1.00 88.37      A    N
ATOM   1528  CZ  ARG A 198      82.832 167.545  24.073  1.00 89.82      A    C
ATOM   1529  NH1 ARG A 198      83.171 166.263  24.164  1.00 90.02      A    N
ATOM   1530  NH2 ARG A 198      83.774 168.482  24.127  1.00 89.71      A    N
ATOM   1531  C   ARG A 198      75.779 166.118  22.271  1.00 79.26      A    C
ATOM   1532  O   ARG A 198      75.801 165.328  21.328  1.00 79.99      A    O
ATOM   1533  N   ARG A 199      74.833 166.110  23.204  1.00 79.41      A    N
ATOM   1534  CA  ARG A 199      73.750 165.140  23.183  1.00 80.27      A    C
ATOM   1535  CB  ARG A 199      73.248 164.900  24.614  1.00 80.89      A    C
ATOM   1536  CG  ARG A 199      74.188 164.018  25.433  1.00 82.79      A    C
ATOM   1537  CD  ARG A 199      74.482 164.560  26.832  1.00 84.19      A    C
ATOM   1538  NE  ARG A 199      73.348 164.467  27.751  1.00 86.52      A    N
ATOM   1539  CZ  ARG A 199      73.448 164.601  29.074  1.00 87.75      A    C
ATOM   1540  NH1 ARG A 199      74.630 164.832  29.635  1.00 87.92      A    N
ATOM   1541  NH2 ARG A 199      72.370 164.506  29.844  1.00 87.41      A    N
ATOM   1542  C   ARG A 199      72.596 165.555  22.270  1.00 80.02      A    C
ATOM   1543  O   ARG A 199      71.734 164.743  21.945  1.00 80.55      A    O
ATOM   1544  N   LEU A 200      72.596 166.811  21.834  1.00 79.96      A    N
ATOM   1545  CA  LEU A 200      71.535 167.321  20.969  1.00 80.20      A    C
ATOM   1546  CB  LEU A 200      71.897 168.718  20.456  1.00 79.61      A    C
ATOM   1547  CG  LEU A 200      70.730 169.626  20.049  1.00 79.11      A    C
ATOM   1548  CD1 LEU A 200      71.248 171.024  19.776  1.00 79.00      A    C
ATOM   1549  CD2 LEU A 200      70.029 169.071  18.829  1.00 79.06      A    C
ATOM   1550  C   LEU A 200      71.218 166.398  19.792  1.00 80.88      A    C
ATOM   1551  O   LEU A 200      70.051 166.200  19.457  1.00 81.14      A    O
ATOM   1552  N   HIS A 201      72.246 165.840  19.160  1.00 82.35      A    N
ATOM   1553  CA  HIS A 201      72.040 164.927  18.031  1.00 83.77      A    C
ATOM   1554  CB  HIS A 201      73.020 165.246  16.894  1.00 85.91      A    C
ATOM   1555  CG  HIS A 201      72.690 166.506  16.151  1.00 88.68      A    C
ATOM   1556  CD2 HIS A 201      73.341 167.691  16.071  1.00 89.00      A    C
ATOM   1557  ND1 HIS A 201      71.547 166.644  15.391  1.00 89.41      A    N
ATOM   1558  CE1 HIS A 201      71.508 167.860  14.875  1.00 89.37      A    C
ATOM   1559  NE2 HIS A 201      72.584 168.516  15.272  1.00 89.99      A    N
ATOM   1560  C   HIS A 201      72.210 163.477  18.483  1.00 83.04      A    C
ATOM   1561  O   HIS A 201      71.458 162.593  18.063  1.00 82.40      A    O
ATOM   1562  N   GLU A 202      73.204 163.251  19.339  1.00 82.11      A    N
ATOM   1563  CA  GLU A 202      73.496 161.933  19.900  1.00 80.69      A    C
ATOM   1564  CB  GLU A 202      74.394 162.110  21.127  1.00 81.79      A    C
ATOM   1565  CG  GLU A 202      74.906 160.837  21.761  1.00 84.81      A    C
ATOM   1566  CD  GLU A 202      75.680 161.113  23.047  1.00 87.19      A    C
ATOM   1567  OE1 GLU A 202      76.711 161.826  22.991  1.00 87.67      A    O
ATOM   1568  OE2 GLU A 202      75.253 160.619  24.115  1.00 87.41      A    O
ATOM   1569  C   GLU A 202      72.166 161.279  20.295  1.00 78.70      A    C
ATOM   1570  O   GLU A 202      71.876 160.146  19.912  1.00 79.59      A    O
ATOM   1571  N   ASN A 203      71.368 162.013  21.066  1.00 75.44      A    N
ATOM   1572  CA  ASN A 203      70.050 161.573  21.511  1.00 72.38      A    C
ATOM   1573  CB  ASN A 203      70.150 160.345  22.425  1.00 74.28      A    C
ATOM   1574  CG  ASN A 203      70.987 160.598  23.656  1.00 75.76      A    C
ATOM   1575  OD1 ASN A 203      72.190 160.844  23.563  1.00 76.47      A    O
ATOM   1576  ND2 ASN A 203      70.352 160.540  24.825  1.00 76.85      A    N
ATOM   1577  C   ASN A 203      69.398 162.747  22.241  1.00 68.68      A    C
ATOM   1578  O   ASN A 203      69.624 162.966  23.430  1.00 68.04      A    O
ATOM   1579  N   PRO A 204      68.579 163.522  21.516  1.00 65.32      A    N
ATOM   1580  CD  PRO A 204      68.205 163.167  20.136  1.00 63.99      A    C
ATOM   1581  CA  PRO A 204      67.837 164.710  21.958  1.00 62.85      A    C
ATOM   1582  CB  PRO A 204      66.851 164.946  20.815  1.00 63.09      A    C
ATOM   1583  CG  PRO A 204      67.588 164.444  19.634  1.00 65.10      A    C
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FIGURE 11-36

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ATOM   1584  C   PRO A 204      67.120 164.631  23.299  1.00 59.92      A    C
ATOM   1585  O   PRO A 204      67.316 165.485  24.158  1.00 56.76      A    O
ATOM   1586  N   LEU A 205      66.272 163.619  23.457  1.00 59.26      A    N
ATOM   1587  CA  LEU A 205      65.490 163.436  24.677  1.00 57.62      A    C
ATOM   1588  CB  LEU A 205      64.930 162.008  24.726  1.00 57.61      A    C
ATOM   1589  CG  LEU A 205      63.882 161.542  23.706  1.00 56.20      A    C
ATOM   1590  CD1 LEU A 205      62.547 162.145  24.029  1.00 55.06      A    C
ATOM   1591  CD2 LEU A 205      64.311 161.913  22.291  1.00 57.88      A    C
ATOM   1592  C   LEU A 205      66.287 163.734  25.956  1.00 57.72      A    C
ATOM   1593  O   LEU A 205      65.745 164.281  26.919  1.00 56.26      A    O
ATOM   1594  N   ARG A 206      67.571 163.385  25.957  1.00 58.21      A    N
ATOM   1595  CA  ARG A 206      68.437 163.619  27.115  1.00 60.02      A    C
ATOM   1596  CB  ARG A 206      69.863 163.156  26.801  1.00 62.79      A    C
ATOM   1597  CG  ARG A 206      70.329 161.930  27.595  1.00 68.46      A    C
ATOM   1598  CD  ARG A 206      70.684 162.287  29.048  1.00 71.63      A    C
ATOM   1599  NE  ARG A 206      69.641 161.949  30.020  1.00 75.30      A    N
ATOM   1600  CZ  ARG A 206      69.313 160.705  30.374  1.00 77.10      A    C
ATOM   1601  NH1 ARG A 206      69.943 159.667  29.835  1.00 78.10      A    N
ATOM   1602  NH2 ARG A 206      68.364 160.496  31.280  1.00 76.03      A    N
ATOM   1603  C   ARG A 206      68.453 165.084  27.562  1.00 59.24      A    C
ATOM   1604  O   ARG A 206      68.590 165.379  28.753  1.00 59.45      A    O
ATOM   1605  N   VAL A 207      68.318 165.997  26.605  1.00 57.88      A    N
ATOM   1606  CA  VAL A 207      68.304 167.427  26.900  1.00 55.96      A    C
ATOM   1607  CB  VAL A 207      68.085 168.260  25.613  1.00 55.54      A    C
ATOM   1608  CG1 VAL A 207      67.961 169.737  25.956  1.00 54.05      A    C
ATOM   1609  CG2 VAL A 207      69.234 168.037  24.649  1.00 54.47      A    C
ATOM   1610  C   VAL A 207      67.190 167.768  27.887  1.00 55.03      A    C
ATOM   1611  O   VAL A 207      67.380 168.580  28.798  1.00 53.63      A    O
ATOM   1612  N   LEU A 208      66.031 167.142  27.697  1.00 53.95      A    N
ATOM   1613  CA  LEU A 208      64.865 167.378  28.546  1.00 53.14      A    C
ATOM   1614  CB  LEU A 208      63.699 166.517  28.069  1.00 49.14      A    C
ATOM   1615  CG  LEU A 208      63.286 166.583  26.596  1.00 48.06      A    C
ATOM   1616  CD1 LEU A 208      62.131 165.616  26.366  1.00 44.36      A    C
ATOM   1617  CD2 LEU A 208      62.880 168.004  26.217  1.00 43.79      A    C
ATOM   1618  C   LEU A 208      65.145 167.062  30.016  1.00 56.19      A    C
ATOM   1619  O   LEU A 208      64.456 167.547  30.918  1.00 55.47      A    O
ATOM   1620  N   ASP A 209      66.162 166.244  30.248  1.00 58.60      A    N
ATOM   1621  CA  ASP A 209      66.523 165.834  31.594  1.00 63.25      A    C
ATOM   1622  CB  ASP A 209      67.227 164.475  31.537  1.00 65.73      A    C
ATOM   1623  CG  ASP A 209      67.507 163.904  32.911  1.00 70.31      A    C
ATOM   1624  OD1 ASP A 209      68.165 164.588  33.732  1.00 73.18      A    O
ATOM   1625  OD2 ASP A 209      67.074 162.759  33.167  1.00 72.65      A    O
ATOM   1626  C   ASP A 209      67.424 166.851  32.275  1.00 64.35      A    C
ATOM   1627  O   ASP A 209      67.322 167.068  33.480  1.00 65.84      A    O
ATOM   1628  N   SER A 210      68.303 167.469  31.493  1.00 66.00      A    N
ATOM   1629  CA  SER A 210      69.251 168.453  31.997  1.00 66.92      A    C
ATOM   1630  CB  SER A 210      69.735 169.350  30.855  1.00 66.58      A    C
ATOM   1631  OG  SER A 210      70.668 170.310  31.324  1.00 67.27      A    O
ATOM   1632  C   SER A 210      68.701 169.319  33.122  1.00 68.04      A    C
ATOM   1633  O   SER A 210      67.615 169.890  33.018  1.00 68.19      A    O
ATOM   1634  N   LYS A 211      69.466 169.412  34.202  1.00 69.67      A    N
ATOM   1635  CA  LYS A 211      69.069 170.218  35.345  1.00 72.13      A    C
ATOM   1636  CB  LYS A 211      69.533 169.554  36.652  1.00 73.31      A    C
ATOM   1637  CG  LYS A 211      68.574 168.487  37.212  1.00 74.22      A    C
ATOM   1638  CD  LYS A 211      68.397 167.293  36.271  1.00 75.60      A    C
ATOM   1639  CE  LYS A 211      67.317 166.320  36.771  1.00 76.29      A    C
ATOM   1640  NZ  LYS A 211      67.652 165.682  38.088  1.00 75.28      A    N
ATOM   1641  C   LYS A 211      69.664 171.617  35.211  1.00 72.41      A    C
ATOM   1642  O   LYS A 211      69.273 172.543  35.923  1.00 72.53      A    O
ATOM   1643  N   ASP A 212      70.603 171.759  34.281  1.00 73.53      A    N
ATOM   1644  CA  ASP A 212      71.267 173.032  34.023  1.00 73.50      A    C
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FIGURE 11-37

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ATOM   1645  CB  ASP A 212      72.236 172.872  32.852  1.00 75.61      A    C
ATOM   1646  CG  ASP A 212      73.080 174.107  32.614  1.00 77.86      A    C
ATOM   1647  OD1 ASP A 212      74.129 173.981  31.948  1.00 78.35      A    O
ATOM   1648  OD2 ASP A 212      72.696 175.202  33.082  1.00 79.49      A    O
ATOM   1649  C   ASP A 212      70.241 174.121  33.721  1.00 73.03      A    C
ATOM   1650  O   ASP A 212      69.482 174.016  32.764  1.00 72.47      A    O
ATOM   1651  N   LYS A 213      70.227 175.162  34.547  1.00 73.25      A    N
ATOM   1652  CA  LYS A 213      69.289 176.275  34.403  1.00 73.82      A    C
ATOM   1653  CB  LYS A 213      69.690 177.404  35.362  1.00 74.12      A    C
ATOM   1654  CG  LYS A 213      68.720 178.575  35.420  1.00 77.03      A    C
ATOM   1655  CD  LYS A 213      69.131 179.577  36.500  1.00 79.22      A    C
ATOM   1656  CE  LYS A 213      68.140 180.739  36.613  1.00 80.57      A    C
ATOM   1657  NZ  LYS A 213      68.546 181.734  37.654  1.00 79.97      A    N
ATOM   1658  C   LYS A 213      69.197 176.810  32.971  1.00 73.46      A    C
ATOM   1659  O   LYS A 213      68.137 177.252  32.523  1.00 73.54      A    O
ATOM   1660  N   LYS A 214      70.313 176.756  32.256  1.00 72.89      A    N
ATOM   1661  CA  LYS A 214      70.388 177.241  30.882  1.00 72.37      A    C
ATOM   1662  CB  LYS A 214      71.838 177.119  30.394  1.00 74.84      A    C
ATOM   1663  CG  LYS A 214      72.221 178.049  29.257  1.00 78.37      A    C
ATOM   1664  CD  LYS A 214      73.734 178.026  29.019  1.00 80.61      A    C
ATOM   1665  CE  LYS A 214      74.146 179.051  27.968  1.00 82.72      A    C
ATOM   1666  NZ  LYS A 214      73.680 180.431  28.312  1.00 83.69      A    N
ATOM   1667  C   LYS A 214      69.443 176.467  29.954  1.00 69.81      A    C
ATOM   1668  O   LYS A 214      68.608 177.055  29.271  1.00 68.04      A    O
ATOM   1669  N   ASP A 215      69.582 175.145  29.940  1.00 67.82      A    N
ATOM   1670  CA  ASP A 215      68.756 174.281  29.105  1.00 65.51      A    C
ATOM   1671  CB  ASP A 215      69.223 172.833  29.235  1.00 66.24      A    C
ATOM   1672  CG  ASP A 215      70.688 172.659  28.882  1.00 68.51      A    C
ATOM   1673  OD1 ASP A 215      71.079 173.033  27.755  1.00 70.20      A    O
ATOM   1674  OD2 ASP A 215      71.451 172.143  29.728  1.00 68.27      A    O
ATOM   1675  C   ASP A 215      67.276 174.360  29.469  1.00 64.23      A    C
ATOM   1676  O   ASP A 215      66.412 174.503  28.595  1.00 63.25      A    O
ATOM   1677  N   LYS A 216      67.001 174.268  30.767  1.00 61.74      A    N
ATOM   1678  CA  LYS A 216      65.642 174.303  31.291  1.00 59.24      A    C
ATOM   1679  CB  LYS A 216      65.671 174.415  32.818  1.00 60.21      A    C
ATOM   1680  CG  LYS A 216      66.371 173.250  33.500  1.00 59.93      A    C
ATOM   1681  CD  LYS A 216      66.053 173.196  34.985  1.00 61.36      A    C
ATOM   1682  CE  LYS A 216      64.573 172.913  35.214  1.00 61.94      A    C
ATOM   1683  NZ  LYS A 216      64.283 172.556  36.626  1.00 63.20      A    N
ATOM   1684  C   LYS A 216      64.817 175.433  30.702  1.00 56.96      A    C
ATOM   1685  O   LYS A 216      63.650 175.246  30.345  1.00 56.96      A    O
ATOM   1686  N   VAL A 217      65.423 176.607  30.605  1.00 54.13      A    N
ATOM   1687  CA  VAL A 217      64.736 177.753  30.037  1.00 51.74      A    C
ATOM   1688  CB  VAL A 217      65.657 178.992  30.012  1.00 51.92      A    C
ATOM   1689  CG1 VAL A 217      64.878 180.219  29.556  1.00 51.58      A    C
ATOM   1690  CG2 VAL A 217      66.247 179.223  31.399  1.00 50.31      A    C
ATOM   1691  C   VAL A 217      64.317 177.403  28.609  1.00 50.68      A    C
ATOM   1692  O   VAL A 217      63.205 177.713  28.190  1.00 50.19      A    O
ATOM   1693  N   ILE A 218      65.210 176.741  27.875  1.00 48.80      A    N
ATOM   1694  CA  ILE A 218      64.936 176.357  26.495  1.00 47.34      A    C
ATOM   1695  CB  ILE A 218      66.242 175.964  25.766  1.00 47.55      A    C
ATOM   1696  CG2 ILE A 218      65.923 175.304  24.414  1.00 44.26      A    C
ATOM   1697  CG1 ILE A 218      67.126 177.206  25.602  1.00 44.34      A    C
ATOM   1698  CD1 ILE A 218      68.477 176.927  24.978  1.00 41.81      A    C
ATOM   1699  C   ILE A 218      63.963 175.187  26.438  1.00 48.41      A    C
ATOM   1700  O   ILE A 218      63.034 175.165  25.617  1.00 46.04      A    O
ATOM   1701  N   VAL A 219      64.191 174.207  27.309  1.00 47.87      A    N
ATOM   1702  CA  VAL A 219      63.338 173.031  27.381  1.00 45.39      A    C
ATOM   1703  CB  VAL A 219      63.864 172.022  28.419  1.00 46.22      A    C
ATOM   1704  CG1 VAL A 219      62.814 170.944  28.685  1.00 45.23      A    C
ATOM   1705  CG2 VAL A 219      65.148 171.385  27.911  1.00 44.98      A    C
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FIGURE 11-38

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ATOM   1706  C   VAL A 219      61.924 173.434  27.763  1.00 45.43      A    C
ATOM   1707  O   VAL A 219      60.962 172.772  27.380  1.00 46.50      A    O
ATOM   1708  N   ALA A 220      61.795 174.525  28.509  1.00 43.99      A    N
ATOM   1709  CA  ALA A 220      60.478 174.988  28.935  1.00 46.92      A    C
ATOM   1710  CB  ALA A 220      60.607 176.292  29.734  1.00 44.24      A    C
ATOM   1711  C   ALA A 220      59.487 175.177  27.780  1.00 49.68      A    C
ATOM   1712  O   ALA A 220      58.280 175.025  27.970  1.00 50.02      A    O
ATOM   1713  N   GLU A 221      59.983 175.518  26.591  1.00 51.83      A    N
ATOM   1714  CA  GLU A 221      59.098 175.712  25.442  1.00 52.57      A    C
ATOM   1715  CB  GLU A 221      59.303 177.106  24.830  1.00 56.57      A    C
ATOM   1716  CG  GLU A 221      58.316 178.166  25.322  1.00 62.91      A    C
ATOM   1717  CD  GLU A 221      58.573 178.614  26.754  1.00 68.08      A    C
ATOM   1718  OE1 GLU A 221      59.629 179.237  27.005  1.00 70.51      A    O
ATOM   1719  OE2 GLU A 221      57.720 178.347  27.633  1.00 70.30      A    O
ATOM   1720  C   GLU A 221      59.279 174.639  24.367  1.00 50.42      A    C
ATOM   1721  O   GLU A 221      58.750 174.756  23.261  1.00 49.92      A    O
ATOM   1722  N   ALA A 222      60.027 173.594  24.696  1.00 48.12      A    N
ATOM   1723  CA  ALA A 222      60.254 172.504  23.760  1.00 48.03      A    C
ATOM   1724  CB  ALA A 222      61.295 171.556  24.319  1.00 45.35      A    C
ATOM   1725  C   ALA A 222      58.951 171.744  23.473  1.00 48.10      A    C
ATOM   1726  O   ALA A 222      57.967 171.861  24.210  1.00 48.50      A    O
ATOM   1727  N   PRO A 223      58.920 170.962  22.384  1.00 47.02      A    N
ATOM   1728  CD  PRO A 223      59.952 170.661  21.374  1.00 45.17      A    C
ATOM   1729  CA  PRO A 223      57.686 170.229  22.102  1.00 45.77      A    C
ATOM   1730  CB  PRO A 223      57.900 169.751  20.667  1.00 43.07      A    C
ATOM   1731  CG  PRO A 223      59.363 169.458  20.653  1.00 42.95      A    C
ATOM   1732  C   PRO A 223      57.560 169.074  23.098  1.00 45.16      A    C
ATOM   1733  O   PRO A 223      58.575 168.543  23.568  1.00 43.52      A    O
ATOM   1734  N   SER A 224      56.322 168.692  23.409  1.00 43.73      A    N
ATOM   1735  CA  SER A 224      56.054 167.605  24.348  1.00 42.05      A    C
ATOM   1736  CB  SER A 224      54.891 167.970  25.273  1.00 42.27      A    C
ATOM   1737  OG  SER A 224      54.543 166.856  26.084  1.00 44.17      A    O
ATOM   1738  C   SER A 224      55.737 166.277  23.676  1.00 41.10      A    C
ATOM   1739  O   SER A 224      54.873 166.194  22.795  1.00 40.44      A    O
ATOM   1740  N   ILE A 225      56.432 165.236  24.115  1.00 40.11      A    N
ATOM   1741  CA  ILE A 225      56.229 163.902  23.582  1.00 40.52      A    C
ATOM   1742  CB  ILE A 225      57.119 162.888  24.317  1.00 40.98      A    C
ATOM   1743  CG2 ILE A 225      56.780 162.891  25.829  1.00 40.55      A    C
ATOM   1744  CG1 ILE A 225      56.940 161.498  23.699  1.00 38.04      A    C
ATOM   1745  CD1 ILE A 225      58.207 160.654  23.728  1.00 32.48      A    C
ATOM   1746  C   ILE A 225      54.764 163.489  23.723  1.00 42.42      A    C
ATOM   1747  O   ILE A 225      54.243 162.727  22.910  1.00 43.16      A    O
ATOM   1748  N   LEU A 226      54.095 164.007  24.749  1.00 43.85      A    N
ATOM   1749  CA  LEU A 226      52.687 163.681  24.976  1.00 45.32      A    C
ATOM   1750  CB  LEU A 226      52.223 164.243  26.323  1.00 43.58      A    C
ATOM   1751  CG  LEU A 226      53.011 163.691  27.511  1.00 43.44      A    C
ATOM   1752  CD1 LEU A 226      52.546 164.365  28.788  1.00 42.05      A    C
ATOM   1753  CD2 LEU A 226      52.834 162.180  27.587  1.00 44.45      A    C
ATOM   1754  C   LEU A 226      51.783 164.195  23.859  1.00 46.11      A    C
ATOM   1755  O   LEU A 226      50.691 163.672  23.645  1.00 45.53      A    O
ATOM   1756  N   ASP A 227      52.234 165.225  23.151  1.00 49.08      A    N
ATOM   1757  CA  ASP A 227      51.452 165.768  22.041  1.00 50.21      A    C
ATOM   1758  CB  ASP A 227      51.689 167.271  21.888  1.00 49.47      A    C
ATOM   1759  CG  ASP A 227      51.092 168.075  23.027  1.00 51.63      A    C
ATOM   1760  OD1 ASP A 227      49.940 167.777  23.414  1.00 54.22      A    O
ATOM   1761  OD2 ASP A 227      51.762 169.012  23.527  1.00 49.68      A    O
ATOM   1762  C   ASP A 227      51.812 165.054  20.735  1.00 50.27      A    C
ATOM   1763  O   ASP A 227      51.213 165.328  19.696  1.00 51.57      A    O
ATOM   1764  N   TYR A 228      52.784 164.141  20.796  1.00 49.24      A    N
ATOM   1765  CA  TYR A 228      53.219 163.387  19.623  1.00 48.49      A    C
ATOM   1766  CB  TYR A 228      54.727 163.583  19.378  1.00 50.61      A    C
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FIGURE 11-39

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ATOM   1767  CG  TYR A 228      55.071 164.934  18.793  1.00 51.72      A    C
ATOM   1768  CD1 TYR A 228      54.916 166.098  19.547  1.00 51.53      A    C
ATOM   1769  CE1 TYR A 228      55.142 167.351  18.995  1.00 52.10      A    C
ATOM   1770  CD2 TYR A 228      55.474 165.056  17.459  1.00 52.50      A    C
ATOM   1771  CE2 TYR A 228      55.704 166.305  16.893  1.00 52.08      A    C
ATOM   1772  CZ  TYR A 228      55.535 167.451  17.666  1.00 54.57      A    C
ATOM   1773  OH  TYR A 228      55.762 168.698  17.122  1.00 53.05      A    O
ATOM   1774  C   TYR A 228      52.918 161.899  19.724  1.00 49.61      A    C
ATOM   1775  O   TYR A 228      53.315 161.121  18.859  1.00 50.68      A    O
ATOM   1776  N   LEU A 229      52.225 161.495  20.784  1.00 50.89      A    N
ATOM   1777  CA  LEU A 229      51.878 160.089  20.956  1.00 51.02      A    C
ATOM   1778  CB  LEU A 229      51.078 159.880  22.248  1.00 48.82      A    C
ATOM   1779  CG  LEU A 229      51.741 160.145  23.602  1.00 46.86      A    C
ATOM   1780  CD1 LEU A 229      50.782 159.678  24.690  1.00 45.65      A    C
ATOM   1781  CD2 LEU A 229      53.069 159.398  23.712  1.00 44.27      A    C
ATOM   1782  C   LEU A 229      51.038 159.617  19.773  1.00 52.31      A    C
ATOM   1783  O   LEU A 229      50.117 160.314  19.347  1.00 52.45      A    O
ATOM   1784  N   ASN A 230      51.356 158.438  19.245  1.00 53.29      A    N
ATOM   1785  CA  ASN A 230      50.603 157.889  18.127  1.00 54.75      A    C
ATOM   1786  CB  ASN A 230      51.497 156.951  17.295  1.00 53.63      A    C
ATOM   1787  CG  ASN A 230      51.674 155.584  17.923  1.00 53.58      A    C
ATOM   1788  OD1 ASN A 230      51.850 155.452  19.129  1.00 53.82      A    O
ATOM   1789  ND2 ASN A 230      51.645 154.553  17.093  1.00 56.08      A    N
ATOM   1790  C   ASN A 230      49.373 157.158  18.685  1.00 56.37      A    C
ATOM   1791  O   ASN A 230      49.239 157.006  19.895  1.00 56.21      A    O
ATOM   1792  N   GLU A 231      48.484 156.718  17.801  1.00 57.69      A    N
ATOM   1793  CA  GLU A 231      47.245 156.036  18.186  1.00 58.95      A    C
ATOM   1794  CB  GLU A 231      46.665 155.290  16.977  1.00 64.39      A    C
ATOM   1795  CG  GLU A 231      46.737 156.051  15.651  1.00 70.76      A    C
ATOM   1796  CD  GLU A 231      47.374 155.219  14.539  1.00 73.99      A    C
ATOM   1797  OE1 GLU A 231      48.619 155.054  14.555  1.00 75.29      A    O
ATOM   1798  OE2 GLU A 231      46.628 154.724  13.658  1.00 74.41      A    O
ATOM   1799  C   GLU A 231      47.332 155.063  19.373  1.00 56.03      A    C
ATOM   1800  O   GLU A 231      46.727 155.291  20.420  1.00 55.11      A    O
ATOM   1801  N   PRO A 232      48.075 153.959  19.223  1.00 53.05      A    N
ATOM   1802  CD  PRO A 232      49.002 153.574  18.145  1.00 52.63      A    C
ATOM   1803  CA  PRO A 232      48.161 153.020  20.343  1.00 52.18      A    C
ATOM   1804  CB  PRO A 232      48.915 151.839  19.738  1.00 49.82      A    C
ATOM   1805  CG  PRO A 232      49.870 152.517  18.819  1.00 52.34      A    C
ATOM   1806  C   PRO A 232      48.851 153.608  21.581  1.00 50.81      A    C
ATOM   1807  O   PRO A 232      48.452 153.321  22.705  1.00 50.39      A    O
ATOM   1808  N   SER A 233      49.878 154.430  21.373  1.00 49.83      A    N
ATOM   1809  CA  SER A 233      50.584 155.048  22.491  1.00 48.09      A    C
ATOM   1810  CB  SER A 233      51.773 155.871  21.998  1.00 45.70      A    C
ATOM   1811  OG  SER A 233      52.805 155.037  21.498  1.00 48.07      A    O
ATOM   1812  C   SER A 233      49.632 155.961  23.252  1.00 49.22      A    C
ATOM   1813  O   SER A 233      49.533 155.893  24.485  1.00 48.50      A    O
ATOM   1814  N   LYS A 234      48.925 156.811  22.513  1.00 47.35      A    N
ATOM   1815  CA  LYS A 234      47.999 157.733  23.135  1.00 47.85      A    C
ATOM   1816  CB  LYS A 234      47.403 158.690  22.102  1.00 49.71      A    C
ATOM   1817  CG  LYS A 234      46.468 159.717  22.718  1.00 52.04      A    C
ATOM   1818  CD  LYS A 234      46.085 160.813  21.742  1.00 55.92      A    C
ATOM   1819  CE  LYS A 234      45.235 161.873  22.444  1.00 59.68      A    C
ATOM   1820  NZ  LYS A 234      44.854 163.024  21.560  1.00 62.15      A    N
ATOM   1821  C   LYS A 234      46.886 156.990  23.848  1.00 48.30      A    C
ATOM   1822  O   LYS A 234      46.452 157.398  24.921  1.00 49.33      A    O
ATOM   1823  N   ALA A 235      46.426 155.895  23.260  1.00 47.24      A    N
ATOM   1824  CA  ALA A 235      45.354 155.124  23.863  1.00 47.65      A    C
ATOM   1825  CB  ALA A 235      44.861 154.074  22.875  1.00 47.76      A    C
ATOM   1826  C   ALA A 235      45.805 154.456  25.170  1.00 47.64      A    C
ATOM   1827  O   ALA A 235      45.038 154.371  26.134  1.00 47.13      A    O
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FIGURE 11-40

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ATOM   1828  N   HIS A 236      47.051 153.992  25.198  1.00 45.43      A    N
ATOM   1829  CA  HIS A 236      47.600 153.325  26.374  1.00 44.75      A    C
ATOM   1830  CB  HIS A 236      48.935 152.672  26.024  1.00 44.69      A    C
ATOM   1831  CG  HIS A 236      49.522 151.854  27.132  1.00 47.07      A    C
ATOM   1832  CD2 HIS A 236      50.354 152.192  28.145  1.00 47.20      A    C
ATOM   1833  ND1 HIS A 236      49.279 150.504  27.270  1.00 48.97      A    N
ATOM   1834  CE1 HIS A 236      49.940 150.043  28.317  1.00 47.58      A    C
ATOM   1835  NE2 HIS A 236      50.600 151.047  28.866  1.00 49.26      A    N
ATOM   1836  C   HIS A 236      47.801 154.315  27.521  1.00 44.38      A    C
ATOM   1837  O   HIS A 236      47.416 154.047  28.657  1.00 43.16      A    O
ATOM   1838  N   PHE A 237      48.403 155.458  27.211  1.00 44.01      A    N
ATOM   1839  CA  PHE A 237      48.665 156.491  28.201  1.00 44.22      A    C
ATOM   1840  CB  PHE A 237      49.430 157.644  27.561  1.00 44.29      A    C
ATOM   1841  CG  PHE A 237      49.853 158.696  28.536  1.00 45.02      A    C
ATOM   1842  CD1 PHE A 237      50.747 158.387  29.567  1.00 47.16      A    C
ATOM   1843  CD2 PHE A 237      49.320 159.978  28.466  1.00 43.93      A    C
ATOM   1844  CE1 PHE A 237      51.100 159.340  30.522  1.00 47.59      A    C
ATOM   1845  CE2 PHE A 237      49.662 160.942  29.412  1.00 48.16      A    C
ATOM   1846  CZ  PHE A 237      50.556 160.624  30.447  1.00 47.82      A    C
ATOM   1847  C   PHE A 237      47.363 157.008  28.792  1.00 46.46      A    C
ATOM   1848  O   PHE A 237      47.239 157.193  30.009  1.00 48.01      A    O
ATOM   1849  N   GLU A 238      46.387 157.244  27.924  1.00 45.83      A    N
ATOM   1850  CA  GLU A 238      45.090 157.736  28.363  1.00 44.55      A    C
ATOM   1851  CB  GLU A 238      44.223 158.049  27.143  1.00 44.71      A    C
ATOM   1852  CG  GLU A 238      43.804 159.500  27.007  1.00 49.12      A    C
ATOM   1853  CD  GLU A 238      43.485 159.874  25.565  1.00 52.99      A    C
ATOM   1854  OE1 GLU A 238      42.773 159.097  24.882  1.00 55.28      A    O
ATOM   1855  OE2 GLU A 238      43.949 160.944  25.114  1.00 54.08      A    O
ATOM   1856  C   GLU A 238      44.399 156.706  29.270  1.00 43.21      A    C
ATOM   1857  O   GLU A 238      43.670 157.072  30.199  1.00 39.96      A    O
ATOM   1858  N   ALA A 239      44.614 155.421  28.993  1.00 41.20      A    N
ATOM   1859  CA  ALA A 239      44.014 154.374  29.822  1.00 41.28      A    C
ATOM   1860  CB  ALA A 239      44.275 152.995  29.223  1.00 38.95      A    C
ATOM   1861  C   ALA A 239      44.664 154.480  31.198  1.00 40.30      A    C
ATOM   1862  O   ALA A 239      43.987 154.502  32.217  1.00 39.34      A    O
ATOM   1863  N   VAL A 240      45.990 154.558  31.206  1.00 39.96      A    N
ATOM   1864  CA  VAL A 240      46.742 154.689  32.443  1.00 38.87      A    C
ATOM   1865  CB  VAL A 240      48.232 154.976  32.149  1.00 37.72      A    C
ATOM   1866  CG1 VAL A 240      48.937 155.529  33.409  1.00 37.23      A    C
ATOM   1867  CG2 VAL A 240      48.910 153.696  31.685  1.00 32.72      A    C
ATOM   1868  C   VAL A 240      46.177 155.813  33.310  1.00 39.91      A    C
ATOM   1869  O   VAL A 240      45.730 155.571  34.428  1.00 39.74      A    O
ATOM   1870  N   THR A 241      46.185 157.034  32.779  1.00 40.88      A    N
ATOM   1871  CA  THR A 241      45.704 158.199  33.509  1.00 42.70      A    C
ATOM   1872  CB  THR A 241      45.959 159.496  32.721  1.00 44.24      A    C
ATOM   1873  OG1 THR A 241      45.151 159.511  31.536  1.00 47.49      A    O
ATOM   1874  CG2 THR A 241      47.425 159.590  32.334  1.00 44.56      A    C
ATOM   1875  C   THR A 241      44.227 158.141  33.869  1.00 42.98      A    C
ATOM   1876  O   THR A 241      43.806 158.703  34.884  1.00 43.26      A    O
ATOM   1877  N   ASP A 242      43.436 157.472  33.040  1.00 42.52      A    N
ATOM   1878  CA  ASP A 242      42.023 157.357  33.327  1.00 43.18      A    C
ATOM   1879  CB  ASP A 242      41.283 156.755  32.138  1.00 48.65      A    C
ATOM   1880  CG  ASP A 242      39.851 156.377  32.471  1.00 56.92      A    C
ATOM   1881  OD1 ASP A 242      39.088 157.263  32.936  1.00 61.27      A    O
ATOM   1882  OD2 ASP A 242      39.485 155.192  32.270  1.00 58.83      A    O
ATOM   1883  C   ASP A 242      41.881 156.465  34.549  1.00 43.08      A    C
ATOM   1884  O   ASP A 242      41.087 156.742  35.446  1.00 42.30      A    O
ATOM   1885  N   MET A 243      42.675 155.402  34.594  1.00 42.32      A    N
ATOM   1886  CA  MET A 243      42.611 154.489  35.715  1.00 43.01      A    C
ATOM   1887  CB  MET A 243      43.300 153.176  35.373  1.00 43.71      A    C
ATOM   1888  CG  MET A 243      42.382 152.212  34.644  1.00 44.82      A    C
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FIGURE 11-41

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ATOM   1889  SD  MET A 243      43.259 150.777  34.012  1.00 53.14      A    S
ATOM   1890  CE  MET A 243      44.131 151.513  32.686  1.00 45.31      A    C
ATOM   1891  C   MET A 243      43.163 155.065  37.007  1.00 41.91      A    C
ATOM   1892  O   MET A 243      42.620 154.786  38.078  1.00 41.64      A    O
ATOM   1893  N   LEU A 244      44.232 155.854  36.917  1.00 38.70      A    N
ATOM   1894  CA  LEU A 244      44.798 156.476  38.109  1.00 38.01      A    C
ATOM   1895  CB  LEU A 244      46.086 157.231  37.765  1.00 35.33      A    C
ATOM   1896  CG  LEU A 244      47.306 156.382  37.399  1.00 31.45      A    C
ATOM   1897  CD1 LEU A 244      48.302 157.227  36.642  1.00 27.54      A    C
ATOM   1898  CD2 LEU A 244      47.927 155.795  38.656  1.00 27.25      A    C
ATOM   1899  C   LEU A 244      43.747 157.449  38.658  1.00 39.12      A    C
ATOM   1900  O   LEU A 244      43.585 157.592  39.873  1.00 39.25      A    O
ATOM   1901  N   ASP A 245      43.030 158.106  37.748  1.00 39.96      A    N
ATOM   1902  CA  ASP A 245      41.983 159.048  38.127  1.00 41.10      A    C
ATOM   1903  CB  ASP A 245      41.346 159.676  36.881  1.00 39.87      A    C
ATOM   1904  CG  ASP A 245      42.235 160.732  36.206  1.00 41.11      A    C
ATOM   1905  OD1 ASP A 245      41.785 161.291  35.183  1.00 38.29      A    O
ATOM   1906  OD2 ASP A 245      43.361 161.016  36.681  1.00 38.84      A    O
ATOM   1907  C   ASP A 245      40.895 158.309  38.914  1.00 44.05      A    C
ATOM   1908  O   ASP A 245      40.509 158.720  40.021  1.00 45.99      A    O
ATOM   1909  N   LEU A 246      40.414 157.212  38.334  1.00 43.44      A    N
ATOM   1910  CA  LEU A 246      39.356 156.406  38.927  1.00 44.76      A    C
ATOM   1911  CB  LEU A 246      38.934 155.311  37.942  1.00 46.02      A    C
ATOM   1912  CG  LEU A 246      38.136 155.895  36.760  1.00 48.83      A    C
ATOM   1913  CD1 LEU A 246      37.873 154.845  35.688  1.00 47.78      A    C
ATOM   1914  CD2 LEU A 246      36.822 156.452  37.290  1.00 48.55      A    C
ATOM   1915  C   LEU A 246      39.702 155.810  40.288  1.00 45.26      A    C
ATOM   1916  O   LEU A 246      38.834 155.668  41.151  1.00 45.88      A    O
ATOM   1917  N   LEU A 247      40.967 155.461  40.484  1.00 44.51      A    N
ATOM   1918  CA  LEU A 247      41.397 154.920  41.761  1.00 42.37      A    C
ATOM   1919  CB  LEU A 247      42.648 154.057  41.595  1.00 40.94      A    C
ATOM   1920  CG  LEU A 247      42.508 152.725  40.863  1.00 40.20      A    C
ATOM   1921  CD1 LEU A 247      43.889 152.057  40.791  1.00 40.80      A    C
ATOM   1922  CD2 LEU A 247      41.509 151.825  41.588  1.00 35.95      A    C
ATOM   1923  C   LEU A 247      41.706 156.101  42.679  1.00 41.79      A    C
ATOM   1924  O   LEU A 247      42.085 155.919  43.833  1.00 37.44      A    O
ATOM   1925  N   GLU A 248      41.542 157.312  42.147  1.00 42.22      A    N
ATOM   1926  CA  GLU A 248      41.796 158.536  42.904  1.00 43.78      A    C
ATOM   1927  CB  GLU A 248      40.787 158.648  44.055  1.00 44.84      A    C
ATOM   1928  CG  GLU A 248      39.400 159.016  43.540  1.00 51.18      A    C
ATOM   1929  CD  GLU A 248      38.302 158.922  44.582  1.00 53.48      A    C
ATOM   1930  OE1 GLU A 248      37.123 159.109  44.205  1.00 56.91      A    O
ATOM   1931  OE2 GLU A 248      38.605 158.666  45.767  1.00 56.74      A    O
ATOM   1932  C   GLU A 248      43.233 158.662  43.412  1.00 42.78      A    C
ATOM   1933  O   GLU A 248      43.497 159.284  44.443  1.00 43.34      A    O
ATOM   1934  N   ILE A 249      44.163 158.065  42.672  1.00 40.91      A    N
ATOM   1935  CA  ILE A 249      45.571 158.141  43.014  1.00 39.47      A    C
ATOM   1936  CB  ILE A 249      46.337 156.946  42.424  1.00 40.06      A    C
ATOM   1937  CG2 ILE A 249      47.844 157.194  42.475  1.00 37.52      A    C
ATOM   1938  CG1 ILE A 249      45.939 155.676  43.172  1.00 37.43      A    C
ATOM   1939  CD1 ILE A 249      46.515 154.412  42.562  1.00 39.78      A    C
ATOM   1940  C   ILE A 249      46.127 159.449  42.436  1.00 38.74      A    C
ATOM   1941  O   ILE A 249      46.105 159.663  41.233  1.00 38.43      A    O
ATOM   1942  N   PRO A 250      46.618 160.349  43.295  1.00 38.60      A    N
ATOM   1943  CD  PRO A 250      46.810 160.262  44.757  1.00 40.25      A    C
ATOM   1944  CA  PRO A 250      47.152 161.602  42.756  1.00 38.89      A    C
ATOM   1945  CB  PRO A 250      47.345 162.459  44.005  1.00 39.14      A    C
ATOM   1946  CG  PRO A 250      47.748 161.431  45.053  1.00 38.07      A    C
ATOM   1947  C   PRO A 250      48.462 161.347  42.019  1.00 38.43      A    C
ATOM   1948  O   PRO A 250      49.233 160.469  42.395  1.00 39.64      A    O
ATOM   1949  N   TYR A 251      48.715 162.105  40.966  1.00 36.82      A    N
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FIGURE 11-42

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ATOM   1950  CA  TYR A 251      49.950 161.932  40.231  1.00 38.11      A    C
ATOM   1951  CB  TYR A 251      49.860 160.716  39.306  1.00 36.94      A    C
ATOM   1952  CG  TYR A 251      48.793 160.880  38.270  1.00 35.42      A    C
ATOM   1953  CD1 TYR A 251      49.080 161.456  37.032  1.00 33.28      A    C
ATOM   1954  CE1 TYR A 251      48.075 161.703  36.113  1.00 35.50      A    C
ATOM   1955  CD2 TYR A 251      47.474 160.549  38.561  1.00 33.83      A    C
ATOM   1956  CE2 TYR A 251      46.463 160.795  37.654  1.00 34.87      A    C
ATOM   1957  CZ  TYR A 251      46.767 161.373  36.435  1.00 34.84      A    C
ATOM   1958  OH  TYR A 251      45.753 161.646  35.561  1.00 36.98      A    O
ATOM   1959  C   TYR A 251      50.253 163.182  39.429  1.00 39.72      A    C
ATOM   1960  O   TYR A 251      49.414 164.066  39.274  1.00 39.06      A    O
ATOM   1961  N   GLU A 252      51.467 163.232  38.907  1.00 42.19      A    N
ATOM   1962  CA  GLU A 252      51.930 164.371  38.154  1.00 42.60      A    C
ATOM   1963  CB  GLU A 252      53.036 165.042  38.955  1.00 46.13      A    C
ATOM   1964  CG  GLU A 252      53.154 166.528  38.812  1.00 49.71      A    C
ATOM   1965  CD  GLU A 252      54.232 167.080  39.726  1.00 53.23      A    C
ATOM   1966  OE1 GLU A 252      55.433 166.938  39.394  1.00 52.30      A    O
ATOM   1967  OE2 GLU A 252      53.872 167.638  40.785  1.00 53.17      A    O
ATOM   1968  C   GLU A 252      52.473 163.876  36.823  1.00 43.46      A    C
ATOM   1969  O   GLU A 252      53.171 162.856  36.757  1.00 42.51      A    O
ATOM   1970  N   ILE A 253      52.141 164.598  35.762  1.00 44.24      A    N
ATOM   1971  CA  ILE A 253      52.607 164.252  34.432  1.00 43.04      A    C
ATOM   1972  CB  ILE A 253      51.509 164.483  33.393  1.00 43.50      A    C
ATOM   1973  CG2 ILE A 253      52.040 164.148  32.007  1.00 43.95      A    C
ATOM   1974  CG1 ILE A 253      50.285 163.631  33.739  1.00 42.76      A    C
ATOM   1975  CD1 ILE A 253      49.077 163.868  32.837  1.00 42.19      A    C
ATOM   1976  C   ILE A 253      53.778 165.169  34.120  1.00 42.76      A    C
ATOM   1977  O   ILE A 253      53.630 166.386  34.138  1.00 43.10      A    O
ATOM   1978  N   ASP A 254      54.942 164.587  33.856  1.00 41.99      A    N
ATOM   1979  CA  ASP A 254      56.142 165.364  33.540  1.00 41.02      A    C
ATOM   1980  CB  ASP A 254      57.229 165.105  34.589  1.00 41.35      A    C
ATOM   1981  CG  ASP A 254      58.457 165.988  34.409  1.00 43.76      A    C
ATOM   1982  OD1 ASP A 254      59.450 165.801  35.159  1.00 45.98      A    O
ATOM   1983  OD2 ASP A 254      58.438 166.872  33.523  1.00 47.92      A    O
ATOM   1984  C   ASP A 254      56.628 164.920  32.159  1.00 38.73      A    C
ATOM   1985  O   ASP A 254      57.327 163.918  32.036  1.00 37.12      A    O
ATOM   1986  N   SER A 255      56.245 165.669  31.131  1.00 38.14      A    N
ATOM   1987  CA  SER A 255      56.616 165.339  29.761  1.00 40.64      A    C
ATOM   1988  CB  SER A 255      55.960 166.307  28.779  1.00 41.15      A    C
ATOM   1989  OG  SER A 255      56.476 167.618  28.925  1.00 45.62      A    O
ATOM   1990  C   SER A 255      58.117 165.352  29.548  1.00 41.47      A    C
ATOM   1991  O   SER A 255      58.613 164.762  28.599  1.00 40.76      A    O
ATOM   1992  N   ASN A 256      58.844 166.012  30.437  1.00 43.91      A    N
ATOM   1993  CA  ASN A 256      60.285 166.066  30.299  1.00 47.74      A    C
ATOM   1994  CB  ASN A 256      60.792 167.448  30.697  1.00 50.34      A    C
ATOM   1995  CG  ASN A 256      60.225 168.533  29.804  1.00 52.44      A    C
ATOM   1996  OD1 ASN A 256      59.976 169.658  30.246  1.00 54.28      A    O
ATOM   1997  ND2 ASN A 256      60.012 168.196  28.531  1.00 50.64      A    N
ATOM   1998  C   ASN A 256      60.976 164.977  31.096  1.00 49.10      A    C
ATOM   1999  O   ASN A 256      62.198 164.815  31.011  1.00 49.33      A    O
ATOM   2000  N   MET A 257      60.203 164.217  31.864  1.00 49.50      A    N
ATOM   2001  CA  MET A 257      60.800 163.129  32.611  1.00 50.36      A    C
ATOM   2002  CB  MET A 257      59.841 162.588  33.666  1.00 52.44      A    C
ATOM   2003  CG  MET A 257      60.524 161.701  34.695  1.00 52.97      A    C
ATOM   2004  SD  MET A 257      59.790 160.076  34.770  1.00 54.19      A    S
ATOM   2005  CE  MET A 257      58.412 160.445  35.825  1.00 55.24      A    C
ATOM   2006  C   MET A 257      61.118 162.050  31.582  1.00 51.20      A    C
ATOM   2007  O   MET A 257      60.227 161.439  30.998  1.00 49.87      A    O
ATOM   2008  N   VAL A 258      62.407 161.870  31.334  1.00 52.96      A    N
ATOM   2009  CA  VAL A 258      62.897 160.884  30.385  1.00 53.44      A    C
ATOM   2010  CB  VAL A 258      63.615 161.565  29.175  1.00 52.19      A    C
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FIGURE 11-43

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ATOM   2011  CG1 VAL A 258      62.677 162.561  28.517  1.00 52.25      A    C
ATOM   2012  CG2 VAL A 258      64.879 162.275  29.627  1.00 51.20      A    C
ATOM   2013  C   VAL A 258      63.883 160.047  31.190  1.00 55.12      A    C
ATOM   2014  O   VAL A 258      64.479 160.537  32.154  1.00 57.11      A    O
ATOM   2015  N   ARG A 259      64.056 158.793  30.806  1.00 54.41      A    N
ATOM   2016  CA  ARG A 259      64.942 157.906  31.537  1.00 55.13      A    C
ATOM   2017  CB  ARG A 259      64.521 157.866  33.018  1.00 55.11      A    C
ATOM   2018  CG  ARG A 259      65.355 156.958  33.929  1.00 56.72      A    C
ATOM   2019  CD  ARG A 259      64.884 157.084  35.389  1.00 55.07      A    C
ATOM   2020  NE  ARG A 259      63.435 156.947  35.458  1.00 53.64      A    N
ATOM   2021  CZ  ARG A 259      62.791 155.788  35.473  1.00 48.85      A    C
ATOM   2022  NH1 ARG A 259      63.469 154.650  35.450  1.00 47.38      A    N
ATOM   2023  NH2 ARG A 259      61.467 155.774  35.450  1.00 47.50      A    N
ATOM   2024  C   ARG A 259      64.731 156.555  30.891  1.00 54.37      A    C
ATOM   2025  O   ARG A 259      63.616 156.249  30.471  1.00 55.90      A    O
ATOM   2026  N   GLY A 260      65.784 155.751  30.803  1.00 52.29      A    N
ATOM   2027  CA  GLY A 260      65.640 154.446  30.184  1.00 51.00      A    C
ATOM   2028  C   GLY A 260      65.207 154.585  28.735  1.00 51.11      A    C
ATOM   2029  O   GLY A 260      64.488 153.737  28.200  1.00 49.52      A    O
ATOM   2030  N   LEU A 261      65.656 155.663  28.099  1.00 51.53      A    N
ATOM   2031  CA  LEU A 261      65.322 155.950  26.705  1.00 53.71      A    C
ATOM   2032  CB  LEU A 261      66.153 157.137  26.209  1.00 52.31      A    C
ATOM   2033  CG  LEU A 261      65.914 158.403  27.025  1.00 51.10      A    C
ATOM   2034  CD1 LEU A 261      66.781 159.520  26.506  1.00 51.73      A    C
ATOM   2035  CD2 LEU A 261      64.436 158.777  26.958  1.00 51.00      A    C
ATOM   2036  C   LEU A 261      65.548 154.756  25.792  1.00 52.51      A    C
ATOM   2037  O   LEU A 261      64.756 154.483  24.898  1.00 52.23      A    O
ATOM   2038  N   ASP A 262      66.633 154.043  26.044  1.00 53.17      A    N
ATOM   2039  CA  ASP A 262      67.000 152.877  25.258  1.00 53.62      A    C
ATOM   2040  CB  ASP A 262      68.408 152.437  25.653  1.00 56.86      A    C
ATOM   2041  CG  ASP A 262      69.472 153.440  25.236  1.00 60.18      A    C
ATOM   2042  OD1 ASP A 262      69.245 154.664  25.381  1.00 62.36      A    O
ATOM   2043  OD2 ASP A 262      70.545 152.998  24.771  1.00 62.14      A    O
ATOM   2044  C   ASP A 262      66.061 151.669  25.337  1.00 52.22      A    C
ATOM   2045  O   ASP A 262      65.932 150.934  24.360  1.00 53.21      A    O
ATOM   2046  N   TYR A 263      65.394 151.464  26.472  1.00 49.69      A    N
ATOM   2047  CA  TYR A 263      64.531 150.289  26.623  1.00 45.91      A    C
ATOM   2048  CB  TYR A 263      65.166 149.335  27.632  1.00 45.72      A    C
ATOM   2049  CG  TYR A 263      65.426 149.975  28.976  1.00 46.21      A    C
ATOM   2050  CD1 TYR A 263      64.437 150.022  29.956  1.00 44.81      A    C
ATOM   2051  CE1 TYR A 263      64.674 150.624  31.182  1.00 46.17      A    C
ATOM   2052  CD2 TYR A 263      66.662 150.549  29.261  1.00 46.02      A    C
ATOM   2053  CE2 TYR A 263      66.909 151.152  30.483  1.00 47.09      A    C
ATOM   2054  CZ  TYR A 263      65.911 151.186  31.440  1.00 46.59      A    C
ATOM   2055  OH  TYR A 263      66.160 151.778  32.650  1.00 45.79      A    O
ATOM   2056  C   TYR A 263      63.065 150.479  26.994  1.00 43.85      A    C
ATOM   2057  O   TYR A 263      62.230 149.646  26.653  1.00 41.94      A    O
ATOM   2058  N   TYR A 264      62.749 151.553  27.702  1.00 42.56      A    N
ATOM   2059  CA  TYR A 264      61.374 151.799  28.111  1.00 43.02      A    C
ATOM   2060  CB  TYR A 264      61.309 152.978  29.079  1.00 41.79      A    C
ATOM   2061  CG  TYR A 264      61.610 152.653  30.519  1.00 44.61      A    C
ATOM   2062  CD1 TYR A 264      62.414 153.508  31.285  1.00 44.29      A    C
ATOM   2063  CE1 TYR A 264      62.652 153.258  32.633  1.00 44.67      A    C
ATOM   2064  CD2 TYR A 264      61.050 151.530  31.141  1.00 43.73      A    C
ATOM   2065  CE2 TYR A 264      61.278 151.270  32.499  1.00 44.64      A    C
ATOM   2066  CZ  TYR A 264      62.079 152.142  33.235  1.00 45.64      A    C
ATOM   2067  OH  TYR A 264      62.284 151.935  34.575  1.00 47.85      A    O
ATOM   2068  C   TYR A 264      60.431 152.097  26.953  1.00 43.01      A    C
ATOM   2069  O   TYR A 264      60.800 152.724  25.960  1.00 45.02      A    O
ATOM   2070  N   THR A 265      59.195 151.662  27.106  1.00 42.16      A    N
ATOM   2071  CA  THR A 265      58.175 151.922  26.115  1.00 43.62      A    C
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FIGURE 11-44

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ATOM   2072  CB  THR A 265      57.824 150.662  25.309  1.00 44.70      A    C
ATOM   2073  OG1 THR A 265      58.941 150.303  24.485  1.00 46.57      A    O
ATOM   2074  CG2 THR A 265      56.639 150.931  24.409  1.00 46.29      A    C
ATOM   2075  C   THR A 265      56.940 152.398  26.851  1.00 43.12      A    C
ATOM   2076  O   THR A 265      56.632 151.924  27.948  1.00 46.64      A    O
ATOM   2077  N   HIS A 266      56.242 153.353  26.259  1.00 41.33      A    N
ATOM   2078  CA  HIS A 266      55.035 153.877  26.862  1.00 41.26      A    C
ATOM   2079  CB  HIS A 266      53.952 152.802  26.834  1.00 39.01      A    C
ATOM   2080  CG  HIS A 266      53.574 152.395  25.447  1.00 43.06      A    C
ATOM   2081  CD2 HIS A 266      52.982 153.093  24.448  1.00 40.31      A    C
ATOM   2082  ND1 HIS A 266      53.904 151.168  24.913  1.00 42.58      A    N
ATOM   2083  CE1 HIS A 266      53.534 151.129  23.645  1.00 42.69      A    C
ATOM   2084  NE2 HIS A 266      52.974 152.286  23.337  1.00 41.05      A    N
ATOM   2085  C   HIS A 266      55.217 154.436  28.277  1.00 40.48      A    C
ATOM   2086  O   HIS A 266      56.007 155.355  28.492  1.00 41.50      A    O
ATOM   2087  N   THR A 267      54.497 153.872  29.234  1.00 38.19      A    N
ATOM   2088  CA  THR A 267      54.534 154.359  30.602  1.00 36.18      A    C
ATOM   2089  CB  THR A 267      53.478 153.645  31.483  1.00 37.66      A    C
ATOM   2090  OG1 THR A 267      52.228 153.578  30.790  1.00 35.85      A    O
ATOM   2091  CG2 THR A 267      53.277 154.414  32.798  1.00 36.57      A    C
ATOM   2092  C   THR A 267      55.838 154.260  31.362  1.00 33.88      A    C
ATOM   2093  O   THR A 267      56.445 153.200  31.437  1.00 35.74      A    O
ATOM   2094  N   ILE A 268      56.275 155.381  31.918  1.00 33.59      A    N
ATOM   2095  CA  ILE A 268      57.448 155.373  32.784  1.00 34.14      A    C
ATOM   2096  CB  ILE A 268      58.704 155.959  32.150  1.00 34.70      A    C
ATOM   2097  CG2 ILE A 268      59.302 154.948  31.189  1.00 35.82      A    C
ATOM   2098  CG1 ILE A 268      58.383 157.305  31.530  1.00 35.73      A    C
ATOM   2099  CD1 ILE A 268      59.630 158.111  31.244  1.00 38.98      A    C
ATOM   2100  C   ILE A 268      57.046 156.230  33.963  1.00 31.03      A    C
ATOM   2101  O   ILE A 268      56.192 157.123  33.830  1.00 27.65      A    O
ATOM   2102  N   PHE A 269      57.661 155.983  35.110  1.00 27.88      A    N
ATOM   2103  CA  PHE A 269      57.272 156.728  36.288  1.00 30.96      A    C
ATOM   2104  CB  PHE A 269      56.018 156.087  36.916  1.00 29.17      A    C
ATOM   2105  CG  PHE A 269      56.334 154.849  37.734  1.00 29.97      A    C
ATOM   2106  CD1 PHE A 269      56.561 153.625  37.111  1.00 27.40      A    C
ATOM   2107  CD2 PHE A 269      56.509 154.941  39.117  1.00 27.48      A    C
ATOM   2108  CE1 PHE A 269      56.960 152.518  37.844  1.00 28.40      A    C
ATOM   2109  CE2 PHE A 269      56.908 153.844  39.862  1.00 28.18      A    C
ATOM   2110  CZ  PHE A 269      57.136 152.630  39.228  1.00 32.39      A    C
ATOM   2111  C   PHE A 269      58.340 156.746  37.361  1.00 31.68      A    C
ATOM   2112  O   PHE A 269      59.272 155.939  37.367  1.00 29.84      A    O
ATOM   2113  N   GLU A 270      58.157 157.667  38.294  1.00 32.65      A    N
ATOM   2114  CA  GLU A 270      59.041 157.773  39.442  1.00 34.38      A    C
ATOM   2115  CB  GLU A 270      60.150 158.800  39.201  1.00 33.58      A    C
ATOM   2116  CG  GLU A 270      61.092 158.431  38.083  1.00 39.77      A    C
ATOM   2117  CD  GLU A 270      62.214 159.440  37.888  1.00 42.12      A    C
ATOM   2118  OE1 GLU A 270      62.862 159.379  36.821  1.00 42.35      A    O
ATOM   2119  OE2 GLU A 270      62.453 160.280  38.791  1.00 40.63      A    O
ATOM   2120  C   GLU A 270      58.182 158.225  40.607  1.00 31.87      A    C
ATOM   2121  O   GLU A 270      57.204 158.939  40.422  1.00 29.87      A    O
ATOM   2122  N   ILE A 271      58.504 157.748  41.796  1.00 31.42      A    N
ATOM   2123  CA  ILE A 271      57.800 158.199  42.978  1.00 32.23      A    C
ATOM   2124  CB  ILE A 271      57.453 157.044  43.923  1.00 32.49      A    C
ATOM   2125  CG2 ILE A 271      57.019 157.605  45.286  1.00 31.85      A    C
ATOM   2126  CG1 ILE A 271      56.319 156.207  43.312  1.00 32.84      A    C
ATOM   2127  CD1 ILE A 271      56.120 154.854  43.974  1.00 29.35      A    C
ATOM   2128  C   ILE A 271      58.855 159.092  43.606  1.00 33.01      A    C
ATOM   2129  O   ILE A 271      59.993 158.672  43.802  1.00 34.41      A    O
ATOM   2130  N   MET A 272      58.514 160.331  43.904  1.00 33.73      A    N
ATOM   2131  CA  MET A 272      59.531 161.194  44.469  1.00 36.83      A    C
ATOM   2132  CB  MET A 272      59.761 162.382  43.541  1.00 40.75      A    C
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FIGURE 11-45

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ATOM   2133  CG  MET A 272      59.942 161.942  42.097  1.00 45.07      A    C
ATOM   2134  SD  MET A 272      60.718 163.201  41.135  1.00 56.85      A    S
ATOM   2135  CE  MET A 272      59.358 164.191  40.631  1.00 51.79      A    C
ATOM   2136  C   MET A 272      59.231 161.680  45.863  1.00 37.48      A    C
ATOM   2137  O   MET A 272      58.084 161.977  46.205  1.00 37.42      A    O
ATOM   2138  N   SER A 273      60.272 161.745  46.678  1.00 36.44      A    N
ATOM   2139  CA  SER A 273      60.102 162.231  48.023  1.00 37.02      A    C
ATOM   2140  CB  SER A 273      61.230 161.756  48.924  1.00 35.76      A    C
ATOM   2141  OG  SER A 273      61.299 162.589  50.073  1.00 37.80      A    O
ATOM   2142  C   SER A 273      60.107 163.742  47.966  1.00 38.67      A    C
ATOM   2143  O   SER A 273      60.936 164.348  47.274  1.00 37.68      A    O
ATOM   2144  N   GLU A 274      59.165 164.347  48.679  1.00 39.90      A    N
ATOM   2145  CA  GLU A 274      59.070 165.795  48.735  1.00 42.93      A    C
ATOM   2146  CB  GLU A 274      57.631 166.247  48.496  1.00 45.93      A    C
ATOM   2147  CG  GLU A 274      57.109 165.912  47.111  1.00 51.75      A    C
ATOM   2148  CD  GLU A 274      55.688 166.410  46.886  1.00 57.06      A    C
ATOM   2149  OE1 GLU A 274      54.777 166.001  47.646  1.00 58.06      A    O
ATOM   2150  OE2 GLU A 274      55.487 167.211  45.946  1.00 59.62      A    O
ATOM   2151  C   GLU A 274      59.552 166.285  50.094  1.00 43.12      A    C
ATOM   2152  O   GLU A 274      59.435 167.465  50.417  1.00 45.78      A    O
ATOM   2153  N   ALA A 275      60.094 165.372  50.889  1.00 44.15      A    N
ATOM   2154  CA  ALA A 275      60.610 165.712  52.211  1.00 44.91      A    C
ATOM   2155  CB  ALA A 275      60.923 164.434  53.001  1.00 41.40      A    C
ATOM   2156  C   ALA A 275      61.874 166.553  52.024  1.00 47.01      A    C
ATOM   2157  O   ALA A 275      62.731 166.229  51.208  1.00 47.39      A    O
ATOM   2158  N   PRO A 276      61.999 167.651  52.780  1.00 51.07      A    N
ATOM   2159  CD  PRO A 276      61.044 168.115  53.807  1.00 51.78      A    C
ATOM   2160  CA  PRO A 276      63.161 168.549  52.698  1.00 52.69      A    C
ATOM   2161  CB  PRO A 276      63.013 169.405  53.950  1.00 53.48      A    C
ATOM   2162  CG  PRO A 276      61.505 169.540  54.055  1.00 53.72      A    C
ATOM   2163  C   PRO A 276      64.535 167.874  52.611  1.00 52.70      A    C
ATOM   2164  O   PRO A 276      65.273 168.083  51.652  1.00 51.45      A    O
ATOM   2165  N   LYS A 277      64.873 167.055  53.599  1.00 54.12      A    N
ATOM   2166  CA  LYS A 277      66.177 166.396  53.606  1.00 55.05      A    C
ATOM   2167  CB  LYS A 277      66.336 165.573  54.882  1.00 57.01      A    C
ATOM   2168  CG  LYS A 277      66.083 166.326  56.172  1.00 58.78      A    C
ATOM   2169  CD  LYS A 277      66.701 165.556  57.333  1.00 63.52      A    C
ATOM   2170  CE  LYS A 277      66.351 166.171  58.681  1.00 66.21      A    C
ATOM   2171  NZ  LYS A 277      64.887 166.059  58.963  1.00 71.17      A    N
ATOM   2172  C   LYS A 277      66.483 165.489  52.404  1.00 55.24      A    C
ATOM   2173  O   LYS A 277      67.608 165.021  52.254  1.00 54.89      A    O
ATOM   2174  N   MET A 278      65.498 165.240  51.547  1.00 54.10      A    N
ATOM   2175  CA  MET A 278      65.711 164.354  50.406  1.00 51.32      A    C
ATOM   2176  CB  MET A 278      64.510 163.417  50.244  1.00 48.90      A    C
ATOM   2177  CG  MET A 278      64.281 162.483  51.414  1.00 43.08      A    C
ATOM   2178  SD  MET A 278      65.746 161.469  51.751  1.00 40.62      A    S
ATOM   2179  CE  MET A 278      65.780 160.478  50.298  1.00 38.00      A    C
ATOM   2180  C   MET A 278      65.950 165.083  49.091  1.00 52.95      A    C
ATOM   2181  O   MET A 278      66.058 164.447  48.038  1.00 51.83      A    O
ATOM   2182  N   GLY A 279      66.026 166.410  49.156  1.00 53.56      A    N
ATOM   2183  CA  GLY A 279      66.237 167.218  47.963  1.00 53.10      A    C
ATOM   2184  C   GLY A 279      67.255 166.713  46.948  1.00 53.47      A    C
ATOM   2185  O   GLY A 279      66.977 166.689  45.747  1.00 53.00      A    O
ATOM   2186  N   ALA A 280      68.432 166.307  47.418  1.00 53.57      A    N
ATOM   2187  CA  ALA A 280      69.482 165.819  46.520  1.00 55.19      A    C
ATOM   2188  CB  ALA A 280      70.855 165.904  47.213  1.00 53.82      A    C
ATOM   2189  C   ALA A 280      69.241 164.398  46.010  1.00 54.50      A    C
ATOM   2190  O   ALA A 280      69.789 164.010  44.983  1.00 55.78      A    O
ATOM   2191  N   GLN A 281      68.422 163.632  46.729  1.00 54.93      A    N
ATOM   2192  CA  GLN A 281      68.096 162.246  46.360  1.00 53.57      A    C
ATOM   2193  CB  GLN A 281      68.609 161.287  47.436  1.00 57.35      A    C
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FIGURE 11-46

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ATOM   2194  CG  GLN A 281      70.086 160.955  47.365  1.00 61.55      A    C
ATOM   2195  CD  GLN A 281      70.560 160.259  48.627  1.00 65.43      A    C
ATOM   2196  OE1 GLN A 281      70.739 160.901  49.666  1.00 68.16      A    O
ATOM   2197  NE2 GLN A 281      70.741 158.940  48.556  1.00 65.52      A    N
ATOM   2198  C   GLN A 281      66.584 162.073  46.241  1.00 50.69      A    C
ATOM   2199  O   GLN A 281      66.006 161.205  46.887  1.00 49.73      A    O
ATOM   2200  N   SER A 282      65.959 162.893  45.401  1.00 48.87      A    N
ATOM   2201  CA  SER A 282      64.507 162.902  45.215  1.00 44.40      A    C
ATOM   2202  CB  SER A 282      64.136 163.927  44.141  1.00 46.84      A    C
ATOM   2203  OG  SER A 282      64.375 165.248  44.592  1.00 53.81      A    O
ATOM   2204  C   SER A 282      63.774 161.607  44.901  1.00 40.35      A    C
ATOM   2205  O   SER A 282      62.813 161.266  45.576  1.00 40.55      A    O
ATOM   2206  N   THR A 283      64.223 160.910  43.865  1.00 37.18      A    N
ATOM   2207  CA  THR A 283      63.612 159.678  43.396  1.00 33.97      A    C
ATOM   2208  CB  THR A 283      64.102 159.374  41.978  1.00 34.43      A    C
ATOM   2209  OG1 THR A 283      63.879 160.530  41.159  1.00 33.50      A    O
ATOM   2210  CG2 THR A 283      63.359 158.182  41.393  1.00 31.30      A    C
ATOM   2211  C   THR A 283      63.847 158.460  44.281  1.00 34.03      A    C
ATOM   2212  O   THR A 283      64.977 158.023  44.485  1.00 30.78      A    O
ATOM   2213  N   ILE A 284      62.759 157.891  44.780  1.00 32.03      A    N
ATOM   2214  CA  ILE A 284      62.879 156.758  45.668  1.00 32.29      A    C
ATOM   2215  CB  ILE A 284      62.162 157.049  46.976  1.00 34.52      A    C
ATOM   2216  CG2 ILE A 284      62.818 158.262  47.639  1.00 34.21      A    C
ATOM   2217  CG1 ILE A 284      60.691 157.345  46.713  1.00 33.87      A    C
ATOM   2218  CD1 ILE A 284      59.915 157.589  47.969  1.00 38.59      A    C
ATOM   2219  C   ILE A 284      62.393 155.467  45.067  1.00 30.94      A    C
ATOM   2220  O   ILE A 284      62.589 154.391  45.634  1.00 32.45      A    O
ATOM   2221  N   CYS A 285      61.776 155.574  43.903  1.00 28.97      A    N
ATOM   2222  CA  CYS A 285      61.297 154.413  43.183  1.00 28.31      A    C
ATOM   2223  CB  CYS A 285      59.930 153.960  43.707  1.00 27.54      A    C
ATOM   2224  SG  CYS A 285      59.243 152.515  42.835  1.00 29.68      A    S
ATOM   2225  C   CYS A 285      61.165 154.806  41.726  1.00 29.45      A    C
ATOM   2226  O   CYS A 285      60.698 155.892  41.418  1.00 29.18      A    O
ATOM   2227  N   ALA A 286      61.573 153.924  40.827  1.00 29.83      A    N
ATOM   2228  CA  ALA A 286      61.441 154.226  39.403  1.00 30.78      A    C
ATOM   2229  CB  ALA A 286      62.677 154.978  38.897  1.00 29.70      A    C
ATOM   2230  C   ALA A 286      61.205 152.967  38.573  1.00 29.03      A    C
ATOM   2231  O   ALA A 286      61.628 151.866  38.931  1.00 27.22      A    O
ATOM   2232  N   GLY A 287      60.484 153.130  37.476  1.00 29.64      A    N
ATOM   2233  CA  GLY A 287      60.227 151.999  36.616  1.00 30.94      A    C
ATOM   2234  C   GLY A 287      59.349 152.401  35.457  1.00 33.01      A    C
ATOM   2235  O   GLY A 287      59.157 153.592  35.182  1.00 33.78      A    O
ATOM   2236  N   GLY A 288      58.811 151.401  34.774  1.00 31.70      A    N
ATOM   2237  CA  GLY A 288      57.951 151.674  33.650  1.00 32.18      A    C
ATOM   2238  C   GLY A 288      57.822 150.443  32.786  1.00 33.34      A    C
ATOM   2239  O   GLY A 288      58.349 149.377  33.099  1.00 31.07      A    O
ATOM   2240  N   ARG A 289      57.118 150.603  31.679  1.00 34.27      A    N
ATOM   2241  CA  ARG A 289      56.898 149.512  30.752  1.00 37.36      A    C
ATOM   2242  CB  ARG A 289      55.566 149.769  30.042  1.00 37.07      A    C
ATOM   2243  CG  ARG A 289      55.231 148.837  28.913  1.00 35.61      A    C
ATOM   2244  CD  ARG A 289      53.801 149.086  28.503  1.00 36.12      A    C
ATOM   2245  NE  ARG A 289      52.860 148.543  29.475  1.00 33.32      A    N
ATOM   2246  CZ  ARG A 289      52.751 147.242  29.725  1.00 37.22      A    C
ATOM   2247  NH1 ARG A 289      53.526 146.379  29.072  1.00 37.55      A    N
ATOM   2248  NH2 ARG A 289      51.868 146.796  30.609  1.00 36.04      A    N
ATOM   2249  C   ARG A 289      58.056 149.392  29.753  1.00 38.37      A    C
ATOM   2250  O   ARG A 289      58.761 150.366  29.470  1.00 37.55      A    O
ATOM   2251  N   TYR A 290      58.256 148.192  29.229  1.00 41.24      A    N
ATOM   2252  CA  TYR A 290      59.321 147.958  28.255  1.00 45.89      A    C
ATOM   2253  CB  TYR A 290      60.668 147.838  28.963  1.00 44.26      A    C
ATOM   2254  CG  TYR A 290      60.711 146.749  29.998  1.00 44.74      A    C
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FIGURE 11-47

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ATOM   2255  CD1 TYR A 290      60.926 145.419  29.633  1.00 45.07      A    C
ATOM   2256  CE1 TYR A 290      60.937 144.407  30.587  1.00 45.22      A    C
ATOM   2257  CD2 TYR A 290      60.507 147.041  31.345  1.00 43.37      A    C
ATOM   2258  CE2 TYR A 290      60.513 146.039  32.306  1.00 45.19      A    C
ATOM   2259  CZ  TYR A 290      60.729 144.728  31.924  1.00 44.31      A    C
ATOM   2260  OH  TYR A 290      60.737 143.745  32.875  1.00 44.53      A    O
ATOM   2261  C   TYR A 290      59.055 146.703  27.437  1.00 48.47      A    C
ATOM   2262  O   TYR A 290      58.395 145.781  27.910  1.00 49.52      A    O
ATOM   2263  N   ASN A 291      59.569 146.681  26.208  1.00 53.85      A    N
ATOM   2264  CA  ASN A 291      59.399 145.548  25.293  1.00 56.71      A    C
ATOM   2265  CB  ASN A 291      58.325 145.855  24.251  1.00 58.11      A    C
ATOM   2266  CG  ASN A 291      57.026 146.328  24.860  1.00 62.39      A    C
ATOM   2267  OD1 ASN A 291      56.163 146.874  24.161  1.00 64.00      A    O
ATOM   2268  ND2 ASN A 291      56.866 146.112  26.164  1.00 63.32      A    N
ATOM   2269  C   ASN A 291      60.705 145.299  24.541  1.00 58.91      A    C
ATOM   2270  O   ASN A 291      60.890 145.815  23.433  1.00 61.45      A    O
ATOM   2271  N   GLY A 292      61.615 144.527  25.121  1.00 58.40      A    N
ATOM   2272  CA  GLY A 292      62.852 144.258  24.417  1.00 56.00      A    C
ATOM   2273  C   GLY A 292      63.893 143.531  25.238  1.00 57.20      A    C
ATOM   2274  O   GLY A 292      64.760 142.855  24.681  1.00 55.92      A    O
ATOM   2275  N   LEU A 293      63.816 143.657  26.560  1.00 56.61      A    N
ATOM   2276  CA  LEU A 293      64.792 143.005  27.423  1.00 57.31      A    C
ATOM   2277  CB  LEU A 293      64.538 143.353  28.891  1.00 56.72      A    C
ATOM   2278  CG  LEU A 293      64.467 144.835  29.254  1.00 57.67      A    C
ATOM   2279  CD1 LEU A 293      64.418 144.957  30.773  1.00 57.84      A    C
ATOM   2280  CD2 LEU A 293      65.665 145.582  28.696  1.00 58.02      A    C
ATOM   2281  C   LEU A 293      64.794 141.494  27.270  1.00 56.75      A    C
ATOM   2282  O   LEU A 293      65.856 140.872  27.239  1.00 56.56      A    O
ATOM   2283  N   VAL A 294      63.607 140.905  27.181  1.00 57.02      A    N
ATOM   2284  CA  VAL A 294      63.503 139.461  27.057  1.00 57.51      A    C
ATOM   2285  CB  VAL A 294      62.045 138.998  27.196  1.00 57.26      A    C
ATOM   2286  CG1 VAL A 294      61.969 137.479  27.082  1.00 57.60      A    C
ATOM   2287  CG2 VAL A 294      61.482 139.461  28.535  1.00 56.21      A    C
ATOM   2288  C   VAL A 294      64.058 139.002  25.717  1.00 59.14      A    C
ATOM   2289  O   VAL A 294      64.924 138.122  25.662  1.00 58.03      A    O
ATOM   2290  N   GLU A 295      63.562 139.603  24.640  1.00 60.64      A    N
ATOM   2291  CA  GLU A 295      64.019 139.259  23.299  1.00 62.59      A    C
ATOM   2292  CB  GLU A 295      63.312 140.148  22.267  1.00 63.17      A    C
ATOM   2293  CG  GLU A 295      63.564 139.767  20.812  1.00 65.30      A    C
ATOM   2294  CD  GLU A 295      62.602 140.453  19.841  1.00 66.63      A    C
ATOM   2295  OE1 GLU A 295      61.380 140.170  19.905  1.00 65.12      A    O
ATOM   2296  OE2 GLU A 295      63.071 141.273  19.015  1.00 67.14      A    O
ATOM   2297  C   GLU A 295      65.535 139.442  23.221  1.00 63.10      A    C
ATOM   2298  O   GLU A 295      66.253 138.596  22.688  1.00 62.76      A    O
ATOM   2299  N   GLU A 296      66.013 140.543  23.787  1.00 64.45      A    N
ATOM   2300  CA  GLU A 296      67.436 140.861  23.790  1.00 66.35      A    C
ATOM   2301  CB  GLU A 296      67.662 142.203  24.501  1.00 68.28      A    C
ATOM   2302  CG  GLU A 296      69.022 142.838  24.249  1.00 71.87      A    C
ATOM   2303  CD  GLU A 296      69.059 144.321  24.609  1.00 74.52      A    C
ATOM   2304  OE1 GLU A 296      70.107 144.967  24.371  1.00 75.25      A    O
ATOM   2305  OE2 GLU A 296      68.042 144.842  25.128  1.00 75.67      A    O
ATOM   2306  C   GLU A 296      68.288 139.774  24.447  1.00 65.77      A    C
ATOM   2307  O   GLU A 296      69.474 139.645  24.145  1.00 66.88      A    O
ATOM   2308  N   LEU A 297      67.688 138.995  25.342  1.00 64.16      A    N
ATOM   2309  CA  LEU A 297      68.419 137.934  26.028  1.00 62.08      A    C
ATOM   2310  CB  LEU A 297      68.124 137.963  27.529  1.00 62.27      A    C
ATOM   2311  CG  LEU A 297      69.081 138.811  28.375  1.00 63.39      A    C
ATOM   2312  CD1 LEU A 297      68.499 139.040  29.757  1.00 61.81      A    C
ATOM   2313  CD2 LEU A 297      70.431 138.108  28.478  1.00 62.46      A    C
ATOM   2314  C   LEU A 297      68.124 136.548  25.471  1.00 60.85      A    C
ATOM   2315  O   LEU A 297      68.410 135.535  26.113  1.00 59.54      A    O
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FIGURE 11-48

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ATOM   2316  N   GLY A 298      67.545 136.509  24.276  1.00 59.30      A    N
ATOM   2317  CA  GLY A 298      67.256 135.235  23.645  1.00 58.34      A    C
ATOM   2318  C   GLY A 298      65.885 134.637  23.890  1.00 57.62      A    C
ATOM   2319  O   GLY A 298      65.650 133.479  23.552  1.00 58.40      A    O
ATOM   2320  N   GLY A 299      64.977 135.409  24.472  1.00 55.94      A    N
ATOM   2321  CA  GLY A 299      63.648 134.888  24.718  1.00 55.07      A    C
ATOM   2322  C   GLY A 299      62.656 135.403  23.697  1.00 54.80      A    C
ATOM   2323  O   GLY A 299      63.036 136.108  22.764  1.00 53.47      A    O
ATOM   2324  N   PRO A 300      61.369 135.060  23.840  1.00 54.23      A    N
ATOM   2325  CD  PRO A 300      60.807 134.138  24.838  1.00 52.94      A    C
ATOM   2326  CA  PRO A 300      60.336 135.515  22.904  1.00 54.41      A    C
ATOM   2327  CB  PRO A 300      59.118 134.670  23.282  1.00 54.19      A    C
ATOM   2328  CG  PRO A 300      59.688 133.517  24.072  1.00 54.74      A    C
ATOM   2329  C   PRO A 300      60.050 137.003  23.116  1.00 55.73      A    C
ATOM   2330  O   PRO A 300      60.473 137.585  24.116  1.00 56.14      A    O
ATOM   2331  N   ASP A 301      59.335 137.619  22.179  1.00 56.50      A    N
ATOM   2332  CA  ASP A 301      58.980 139.024  22.327  1.00 56.43      A    C
ATOM   2333  CB  ASP A 301      58.275 139.548  21.075  1.00 59.26      A    C
ATOM   2334  CG  ASP A 301      57.826 140.990  21.225  1.00 63.39      A    C
ATOM   2335  OD1 ASP A 301      58.697 141.870  21.444  1.00 64.29      A    O
ATOM   2336  OD2 ASP A 301      56.601 141.241  21.132  1.00 64.94      A    O
ATOM   2337  C   ASP A 301      58.025 139.046  23.513  1.00 54.19      A    C
ATOM   2338  O   ASP A 301      56.901 138.538  23.434  1.00 54.13      A    O
ATOM   2339  N   THR A 302      58.473 139.620  24.620  1.00 50.63      A    N
ATOM   2340  CA  THR A 302      57.642 139.639  25.813  1.00 47.04      A    C
ATOM   2341  CB  THR A 302      58.256 138.741  26.903  1.00 46.01      A    C
ATOM   2342  OG1 THR A 302      58.765 137.550  26.295  1.00 47.15      A    O
ATOM   2343  CG2 THR A 302      57.211 138.358  27.960  1.00 44.34      A    C
ATOM   2344  C   THR A 302      57.463 141.034  26.381  1.00 45.07      A    C
ATOM   2345  O   THR A 302      58.435 141.726  26.673  1.00 45.13      A    O
ATOM   2346  N   PRO A 303      56.208 141.475  26.524  1.00 44.04      A    N
ATOM   2347  CD  PRO A 303      54.957 140.852  26.055  1.00 42.41      A    C
ATOM   2348  CA  PRO A 303      55.956 142.806  27.080  1.00 41.48      A    C
ATOM   2349  CB  PRO A 303      54.455 143.001  26.862  1.00 42.24      A    C
ATOM   2350  CG  PRO A 303      54.133 142.066  25.710  1.00 43.10      A    C
ATOM   2351  C   PRO A 303      56.305 142.706  28.561  1.00 40.29      A    C
ATOM   2352  O   PRO A 303      56.231 141.624  29.145  1.00 39.22      A    O
ATOM   2353  N   GLY A 304      56.692 143.822  29.167  1.00 40.13      A    N
ATOM   2354  CA  GLY A 304      57.049 143.802  30.573  1.00 37.12      A    C
ATOM   2355  C   GLY A 304      56.903 145.149  31.249  1.00 37.26      A    C
ATOM   2356  O   GLY A 304      56.808 146.192  30.603  1.00 37.59      A    O
ATOM   2357  N   PHE A 305      56.864 145.111  32.571  1.00 35.58      A    N
ATOM   2358  CA  PHE A 305      56.734 146.299  33.381  1.00 33.90      A    C
ATOM   2359  CB  PHE A 305      55.266 146.604  33.668  1.00 32.20      A    C
ATOM   2360  CG  PHE A 305      55.019 148.036  34.099  1.00 30.18      A    C
ATOM   2361  CD1 PHE A 305      54.535 148.966  33.202  1.00 26.73      A    C
ATOM   2362  CD2 PHE A 305      55.319 148.450  35.397  1.00 29.74      A    C
ATOM   2363  CE1 PHE A 305      54.356 150.286  33.582  1.00 30.41      A    C
ATOM   2364  CE2 PHE A 305      55.146 149.763  35.787  1.00 25.82      A    C
ATOM   2365  CZ  PHE A 305      54.667 150.686  34.883  1.00 30.51      A    C
ATOM   2366  C   PHE A 305      57.466 145.999  34.683  1.00 35.83      A    C
ATOM   2367  O   PHE A 305      57.504 144.856  35.143  1.00 34.86      A    O
ATOM   2368  N   GLY A 306      58.074 147.020  35.266  1.00 34.91      A    N
ATOM   2369  CA  GLY A 306      58.783 146.793  36.499  1.00 34.53      A    C
ATOM   2370  C   GLY A 306      59.196 148.100  37.118  1.00 34.39      A    C
ATOM   2371  O   GLY A 306      58.876 149.181  36.621  1.00 34.00      A    O
ATOM   2372  N   PHE A 307      59.891 147.992  38.235  1.00 32.55      A    N
ATOM   2373  CA  PHE A 307      60.397 149.153  38.921  1.00 32.11      A    C
ATOM   2374  CB  PHE A 307      59.265 149.947  39.630  1.00 32.70      A    C
ATOM   2375  CG  PHE A 307      58.664 149.262  40.849  1.00 31.91      A    C
ATOM   2376  CD1 PHE A 307      59.461 148.837  41.913  1.00 31.37      A    C
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FIGURE 11-49

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ATOM   2377  CD2 PHE A 307      57.289 149.103  40.954  1.00 31.03      A    C
ATOM   2378  CE1 PHE A 307      58.892 148.263  43.067  1.00 32.45      A    C
ATOM   2379  CE2 PHE A 307      56.711 148.534  42.093  1.00 32.52      A    C
ATOM   2380  CZ  PHE A 307      57.517 148.112  43.155  1.00 31.91      A    C
ATOM   2381  C   PHE A 307      61.426 148.663  39.906  1.00 30.77      A    C
ATOM   2382  O   PHE A 307      61.503 147.479  40.220  1.00 30.80      A    O
ATOM   2383  N   GLY A 308      62.233 149.580  40.393  1.00 32.67      A    N
ATOM   2384  CA  GLY A 308      63.230 149.198  41.363  1.00 29.73      A    C
ATOM   2385  C   GLY A 308      63.340 150.369  42.286  1.00 29.38      A    C
ATOM   2386  O   GLY A 308      62.965 151.491  41.935  1.00 27.34      A    O
ATOM   2387  N   MET A 309      63.836 150.098  43.480  1.00 32.08      A    N
ATOM   2388  CA  MET A 309      64.034 151.129  44.481  1.00 31.75      A    C
ATOM   2389  CB  MET A 309      62.779 151.252  45.357  1.00 34.53      A    C
ATOM   2390  CG  MET A 309      62.273 149.936  45.928  1.00 37.28      A    C
ATOM   2391  SD  MET A 309      60.605 150.066  46.689  1.00 40.85      A    S
ATOM   2392  CE  MET A 309      59.769 150.962  45.514  1.00 36.90      A    C
ATOM   2393  C   MET A 309      65.251 150.686  45.293  1.00 29.79      A    C
ATOM   2394  O   MET A 309      65.481 149.493  45.463  1.00 28.50      A    O
ATOM   2395  N   GLY A 310      66.061 151.638  45.735  1.00 29.33      A    N
ATOM   2396  CA  GLY A 310      67.223 151.280  46.523  1.00 28.86      A    C
ATOM   2397  C   GLY A 310      66.770 151.305  47.965  1.00 29.64      A    C
ATOM   2398  O   GLY A 310      66.049 152.213  48.368  1.00 30.13      A    O
ATOM   2399  N   ILE A 311      67.166 150.311  48.744  1.00 30.27      A    N
ATOM   2400  CA  ILE A 311      66.754 150.266  50.134  1.00 30.93      A    C
ATOM   2401  CB  ILE A 311      67.040 148.895  50.763  1.00 30.44      A    C
ATOM   2402  CG2 ILE A 311      66.501 148.863  52.180  1.00 25.75      A    C
ATOM   2403  CG1 ILE A 311      66.412 147.796  49.904  1.00 27.85      A    C
ATOM   2404  CD1 ILE A 311      66.253 146.458  50.600  1.00 27.79      A    C
ATOM   2405  C   ILE A 311      67.446 151.329  50.963  1.00 34.55      A    C
ATOM   2406  O   ILE A 311      66.845 151.896  51.889  1.00 36.97      A    O
ATOM   2407  N   GLU A 312      68.714 151.593  50.648  1.00 34.50      A    N
ATOM   2408  CA  GLU A 312      69.461 152.597  51.385  1.00 33.17      A    C
ATOM   2409  CB  GLU A 312      70.864 152.781  50.790  1.00 34.30      A    C
ATOM   2410  CG  GLU A 312      71.869 151.669  51.135  1.00 34.87      A    C
ATOM   2411  CD  GLU A 312      71.758 150.455  50.236  1.00 34.11      A    C
ATOM   2412  OE1 GLU A 312      72.576 149.525  50.397  1.00 34.77      A    O
ATOM   2413  OE2 GLU A 312      70.853 150.421  49.372  1.00 37.49      A    O
ATOM   2414  C   GLU A 312      68.696 153.914  51.331  1.00 32.66      A    C
ATOM   2415  O   GLU A 312      68.522 154.578  52.349  1.00 32.96      A    O
ATOM   2416  N   ARG A 313      68.214 154.273  50.144  1.00 30.75      A    N
ATOM   2417  CA  ARG A 313      67.481 155.516  49.990  1.00 29.93      A    C
ATOM   2418  CB  ARG A 313      67.384 155.910  48.521  1.00 33.03      A    C
ATOM   2419  CG  ARG A 313      66.731 157.265  48.313  1.00 33.35      A    C
ATOM   2420  CD  ARG A 313      66.897 157.722  46.893  1.00 36.15      A    C
ATOM   2421  NE  ARG A 313      68.304 157.831  46.524  1.00 39.64      A    N
ATOM   2422  CZ  ARG A 313      68.732 158.189  45.316  1.00 42.79      A    C
ATOM   2423  NH1 ARG A 313      67.859 158.473  44.360  1.00 41.24      A    N
ATOM   2424  NH2 ARG A 313      70.032 158.260  45.059  1.00 42.99      A    N
ATOM   2425  C   ARG A 313      66.089 155.464  50.601  1.00 29.83      A    C
ATOM   2426  O   ARG A 313      65.580 156.480  51.042  1.00 33.74      A    O
ATOM   2427  N   VAL A 314      65.453 154.300  50.611  1.00 29.74      A    N
ATOM   2428  CA  VAL A 314      64.134 154.192  51.232  1.00 30.28      A    C
ATOM   2429  CB  VAL A 314      63.527 152.773  51.045  1.00 31.88      A    C
ATOM   2430  CG1 VAL A 314      62.326 152.579  51.976  1.00 30.34      A    C
ATOM   2431  CG2 VAL A 314      63.120 152.567  49.587  1.00 28.74      A    C
ATOM   2432  C   VAL A 314      64.327 154.467  52.731  1.00 27.83      A    C
ATOM   2433  O   VAL A 314      63.555 155.184  53.350  1.00 28.01      A    O
ATOM   2434  N   LEU A 315      65.380 153.902  53.303  1.00 31.56      A    N
ATOM   2435  CA  LEU A 315      65.664 154.094  54.722  1.00 31.02      A    C
ATOM   2436  CB  LEU A 315      66.840 153.226  55.145  1.00 28.88      A    C
ATOM   2437  CG  LEU A 315      66.520 151.746  55.282  1.00 27.77      A    C
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FIGURE 11-50

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ATOM   2438  CD1 LEU A 315      67.817 150.962  55.457  1.00 30.64      A    C
ATOM   2439  CD2 LEU A 315      65.595 151.541  56.470  1.00 26.60      A    C
ATOM   2440  C   LEU A 315      65.993 155.546  54.982  1.00 32.57      A    C
ATOM   2441  O   LEU A 315      65.662 156.086  56.033  1.00 32.37      A    O
ATOM   2442  N   LEU A 316      66.644 156.184  54.016  1.00 34.44      A    N
ATOM   2443  CA  LEU A 316      67.006 157.582  54.164  1.00 36.10      A    C
ATOM   2444  CB  LEU A 316      67.889 158.034  53.002  1.00 40.09      A    C
ATOM   2445  CG  LEU A 316      68.849 159.161  53.377  1.00 45.62      A    C
ATOM   2446  CD1 LEU A 316      69.998 158.582  54.214  1.00 45.44      A    C
ATOM   2447  CD2 LEU A 316      69.397 159.825  52.120  1.00 49.23      A    C
ATOM   2448  C   LEU A 316      65.729 158.412  54.194  1.00 37.36      A    C
ATOM   2449  O   LEU A 316      65.611 159.364  54.976  1.00 39.28      A    O
ATOM   2450  N   THR A 317      64.772 158.051  53.341  1.00 35.16      A    N
ATOM   2451  CA  THR A 317      63.493 158.748  53.289  1.00 34.91      A    C
ATOM   2452  CB  THR A 317      62.626 158.212  52.161  1.00 36.35      A    C
ATOM   2453  OG1 THR A 317      63.336 158.327  50.924  1.00 38.69      A    O
ATOM   2454  CG2 THR A 317      61.334 158.997  52.082  1.00 35.71      A    C
ATOM   2455  C   THR A 317      62.725 158.556  54.600  1.00 34.27      A    C
ATOM   2456  O   THR A 317      62.055 159.457  55.083  1.00 35.42      A    O
ATOM   2457  N   MET A 318      62.805 157.364  55.165  1.00 33.83      A    N
ATOM   2458  CA  MET A 318      62.123 157.107  56.419  1.00 36.84      A    C
ATOM   2459  CB  MET A 318      62.274 155.642  56.805  1.00 31.93      A    C
ATOM   2460  CG  MET A 318      61.442 154.745  55.934  1.00 31.30      A    C
ATOM   2461  SD  MET A 318      61.585 153.054  56.433  1.00 36.76      A    S
ATOM   2462  CE  MET A 318      60.544 153.020  57.914  1.00 34.65      A    C
ATOM   2463  C   MET A 318      62.693 158.022  57.504  1.00 38.07      A    C
ATOM   2464  O   MET A 318      61.952 158.579  58.313  1.00 37.80      A    O
ATOM   2465  N   GLU A 319      64.012 158.188  57.487  1.00 38.17      A    N
ATOM   2466  CA  GLU A 319      64.706 159.042  58.431  1.00 38.25      A    C
ATOM   2467  CB  GLU A 319      66.216 158.878  58.221  1.00 42.80      A    C
ATOM   2468  CG  GLU A 319      67.136 159.780  59.019  1.00 49.46      A    C
ATOM   2469  CD  GLU A 319      68.613 159.467  58.748  1.00 56.72      A    C
ATOM   2470  OE1 GLU A 319      69.462 160.377  58.902  1.00 60.19      A    O
ATOM   2471  OE2 GLU A 319      68.931 158.306  58.382  1.00 58.74      A    O
ATOM   2472  C   GLU A 319      64.263 160.489  58.213  1.00 36.58      A    C
ATOM   2473  O   GLU A 319      63.900 161.182  59.156  1.00 34.71      A    O
ATOM   2474  N   ALA A 320      64.267 160.939  56.964  1.00 35.42      A    N
ATOM   2475  CA  ALA A 320      63.858 162.305  56.664  1.00 33.02      A    C
ATOM   2476  CB  ALA A 320      63.930 162.546  55.173  1.00 33.83      A    C
ATOM   2477  C   ALA A 320      62.449 162.615  57.178  1.00 34.03      A    C
ATOM   2478  O   ALA A 320      62.190 163.704  57.689  1.00 33.77      A    O
ATOM   2479  N   GLU A 321      61.534 161.666  57.033  1.00 34.30      A    N
ATOM   2480  CA  GLU A 321      60.159 161.864  57.483  1.00 34.08      A    C
ATOM   2481  CB  GLU A 321      59.192 161.056  56.613  1.00 33.31      A    C
ATOM   2482  CG  GLU A 321      59.013 161.630  55.222  1.00 36.38      A    C
ATOM   2483  CD  GLU A 321      57.783 161.084  54.508  1.00 39.21      A    C
ATOM   2484  OE1 GLU A 321      56.719 160.927  55.161  1.00 36.21      A    O
ATOM   2485  OE2 GLU A 321      57.882 160.828  53.288  1.00 40.21      A    O
ATOM   2486  C   GLU A 321      59.997 161.456  58.932  1.00 35.39      A    C
ATOM   2487  O   GLU A 321      58.891 161.416  59.462  1.00 34.25      A    O
ATOM   2488  N   GLU A 322      61.112 161.140  59.570  1.00 38.47      A    N
ATOM   2489  CA  GLU A 322      61.097 160.729  60.961  1.00 40.60      A    C
ATOM   2490  CB  GLU A 322      60.845 161.935  61.858  1.00 43.20      A    C
ATOM   2491  CG  GLU A 322      61.803 163.073  61.562  1.00 49.16      A    C
ATOM   2492  CD  GLU A 322      61.903 164.054  62.706  1.00 54.05      A    C
ATOM   2493  OE1 GLU A 322      60.844 164.549  63.161  1.00 53.45      A    O
ATOM   2494  OE2 GLU A 322      63.047 164.325  63.145  1.00 56.93      A    O
ATOM   2495  C   GLU A 322      60.055 159.664  61.207  1.00 40.44      A    C
ATOM   2496  O   GLU A 322      59.207 159.792  62.089  1.00 41.26      A    O
ATOM   2497  N   VAL A 323      60.123 158.610  60.406  1.00 40.01      A    N
ATOM   2498  CA  VAL A 323      59.209 157.497  60.535  1.00 41.17      A    C
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FIGURE 11-51

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ATOM   2499  CB  VAL A 323      59.152 156.667  59.260  1.00 38.03      A    C
ATOM   2500  CG1 VAL A 323      58.202 155.513  59.449  1.00 36.51      A    C
ATOM   2501  CG2 VAL A 323      58.737 157.531  58.112  1.00 36.44      A    C
ATOM   2502  C   VAL A 323      59.723 156.591  61.629  1.00 43.20      A    C
ATOM   2503  O   VAL A 323      60.901 156.247  61.652  1.00 44.81      A    O
ATOM   2504  N   VAL A 324      58.849 156.199  62.538  1.00 45.82      A    N
ATOM   2505  CA  VAL A 324      59.284 155.311  63.598  1.00 49.34      A    C
ATOM   2506  CB  VAL A 324      58.828 155.817  65.004  1.00 52.34      A    C
ATOM   2507  CG1 VAL A 324      57.305 155.694  65.160  1.00 52.67      A    C
ATOM   2508  CG2 VAL A 324      59.557 155.043  66.086  1.00 52.68      A    C
ATOM   2509  C   VAL A 324      58.701 153.938  63.308  1.00 49.76      A    C
ATOM   2510  O   VAL A 324      57.480 153.753  63.281  1.00 48.00      A    O
ATOM   2511  N   ILE A 325      59.584 152.984  63.050  1.00 51.51      A    N
ATOM   2512  CA  ILE A 325      59.157 151.628  62.760  1.00 54.07      A    C
ATOM   2513  CB  ILE A 325      60.346 150.721  62.391  1.00 53.58      A    C
ATOM   2514  CG2 ILE A 325      61.246 151.417  61.377  1.00 52.49      A    C
ATOM   2515  CG1 ILE A 325      61.139 150.387  63.652  1.00 51.64      A    C
ATOM   2516  CD1 ILE A 325      62.242 149.423  63.427  1.00 55.19      A    C
ATOM   2517  C   ILE A 325      58.505 151.044  64.008  1.00 55.55      A    C
ATOM   2518  O   ILE A 325      58.787 151.465  65.125  1.00 53.06      A    O
ATOM   2519  N   PRO A 326      57.624 150.059  63.823  1.00 59.09      A    N
ATOM   2520  CD  PRO A 326      57.215 149.507  62.520  1.00 60.93      A    C
ATOM   2521  CA  PRO A 326      56.921 149.390  64.917  1.00 61.43      A    C
ATOM   2522  CB  PRO A 326      56.328 148.167  64.236  1.00 60.84      A    C
ATOM   2523  CG  PRO A 326      55.981 148.702  62.884  1.00 62.11      A    C
ATOM   2524  C   PRO A 326      57.890 149.012  66.027  1.00 63.93      A    C
ATOM   2525  O   PRO A 326      58.905 148.351  65.784  1.00 63.73      A    O
ATOM   2526  N   ALA A 327      57.574 149.442  67.243  1.00 66.36      A    N
ATOM   2527  CA  ALA A 327      58.408 149.149  68.400  1.00 68.74      A    C
ATOM   2528  CB  ALA A 327      57.936 149.971  69.595  1.00 68.74      A    C
ATOM   2529  C   ALA A 327      58.354 147.657  68.732  1.00 70.40      A    C
ATOM   2530  O   ALA A 327      57.310 147.017  68.573  1.00 69.30      A    O
ATOM   2531  N   LEU A 328      59.488 147.107  69.173  1.00 73.20      A    N
ATOM   2532  CA  LEU A 328      59.569 145.698  69.555  1.00 74.59      A    C
ATOM   2533  CB  LEU A 328      60.931 145.378  70.172  1.00 75.07      A    C
ATOM   2534  CG  LEU A 328      62.039 144.913  69.229  1.00 76.50      A    C
ATOM   2535  CD1 LEU A 328      62.163 145.872  68.050  1.00 75.64      A    C
ATOM   2536  CD2 LEU A 328      63.348 144.812  70.015  1.00 76.08      A    C
ATOM   2537  C   LEU A 328      58.486 145.420  70.581  1.00 75.82      A    C
ATOM   2538  O   LEU A 328      58.412 146.084  71.615  1.00 75.99      A    O
ATOM   2539  N   SER A 329      57.641 144.442  70.291  1.00 77.49      A    N
ATOM   2540  CA  SER A 329      56.558 144.102  71.196  1.00 78.81      A    C
ATOM   2541  CB  SER A 329      55.225 144.034  70.438  1.00 80.16      A    C
ATOM   2542  OG  SER A 329      55.208 142.955  69.517  1.00 80.12      A    O
ATOM   2543  C   SER A 329      56.849 142.762  71.824  1.00 79.19      A    C
ATOM   2544  O   SER A 329      56.353 141.736  71.349  1.00 79.27      A    O
ATOM   2545  N   GLU A 330      57.656 142.759  72.882  1.00 79.27      A    N
ATOM   2546  CA  GLU A 330      57.974 141.494  73.533  1.00 79.35      A    C
ATOM   2547  CB  GLU A 330      59.012 140.721  72.704  1.00 80.23      A    C
ATOM   2548  CG  GLU A 330      60.265 141.511  72.364  1.00 81.64      A    C
ATOM   2549  CD  GLU A 330      61.532 140.754  72.707  1.00 81.13      A    C
ATOM   2550  OE1 GLU A 330      61.685 139.606  72.236  1.00 79.13      A    O
ATOM   2551  OE2 GLU A 330      62.373 141.310  73.447  1.00 81.43      A    O
ATOM   2552  C   GLU A 330      58.424 141.537  74.988  1.00 77.45      A    C
ATOM   2553  O   GLU A 330      58.095 142.452  75.746  1.00 77.98      A    O
ATOM   2554  N   LEU A 331      59.184 140.509  75.348  1.00 76.07      A    N
ATOM   2555  CA  LEU A 331      59.702 140.297  76.691  1.00 72.65      A    C
ATOM   2556  CB  LEU A 331      60.637 141.419  77.124  1.00 72.00      A    C
ATOM   2557  CG  LEU A 331      61.322 140.943  78.410  1.00 73.09      A    C
ATOM   2558  CD1 LEU A 331      62.036 139.614  78.170  1.00 72.60      A    C
ATOM   2559  CD2 LEU A 331      62.291 141.979  78.881  1.00 74.70      A    C
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FIGURE 11-52

ATOM	2560	C	LEU	A	331	58.581	140.137	77.709	1.00	69.82	A C
ATOM	2561	O	LEU	A	331	58.263	141.056	78.471	1.00	69.20	A O
ATOM	2562	N	ASP	A	332	57.979	138.955	77.701	1.00	67.11	A N
ATOM	2563	CA	ASP	A	332	56.900	138.640	78.619	1.00	64.40	A C
ATOM	2564	CB	ASP	A	332	56.233	137.323	78.220	1.00	65.68	A C
ATOM	2565	CG	ASP	A	332	55.517	137.413	76.889	1.00	67.52	A C
ATOM	2566	OD1	ASP	A	332	54.654	138.302	76.745	1.00	69.59	A O
ATOM	2567	OD2	ASP	A	332	55.809	136.594	75.990	1.00	68.66	A O
ATOM	2568	C	ASP	A	332	57.465	138.509	80.020	1.00	62.06	A C
ATOM	2569	O	ASP	A	332	56.801	138.840	81.008	1.00	61.93	A O
ATOM	2570	N	ALA	A	333	58.702	138.037	80.109	1.00	58.87	A N
ATOM	2571	CA	ALA	A	333	59.307	137.855	81.414	1.00	57.13	A C
ATOM	2572	CB	ALA	A	333	58.757	136.576	82.063	1.00	56.82	A C
ATOM	2573	C	ALA	A	333	60.823	137.820	81.426	1.00	54.66	A C
ATOM	2574	O	ALA	A	333	61.476	137.442	80.450	1.00	53.18	A O
ATOM	2575	N	TYR	A	334	61.367	138.218	82.568	1.00	51.72	A N
ATOM	2576	CA	TYR	A	334	62.796	138.232	82.780	1.00	49.75	A C
ATOM	2577	CB	TYR	A	334	63.306	139.663	82.932	1.00	47.65	A C
ATOM	2578	CG	TYR	A	334	64.798	139.741	82.797	1.00	48.54	A C
ATOM	2579	CD1	TYR	A	334	65.402	139.844	81.540	1.00	46.57	A C
ATOM	2580	CE1	TYR	A	334	66.792	139.844	81.407	1.00	47.38	A C
ATOM	2581	CD2	TYR	A	334	65.618	139.640	83.919	1.00	48.41	A C
ATOM	2582	CE2	TYR	A	334	67.003	139.636	83.802	1.00	49.97	A C
ATOM	2583	CZ	TYR	A	334	67.586	139.738	82.546	1.00	50.17	A C
ATOM	2584	OH	TYR	A	334	68.962	139.732	82.448	1.00	52.56	A O
ATOM	2585	C	TYR	A	334	63.062	137.463	84.062	1.00	48.97	A C
ATOM	2586	O	TYR	A	334	62.512	137.781	85.114	1.00	49.89	A O
ATOM	2587	N	VAL	A	335	63.908	136.448	83.975	1.00	48.76	A N
ATOM	2588	CA	VAL	A	335	64.234	135.637	85.135	1.00	46.66	A C
ATOM	2589	CB	VAL	A	335	64.361	134.163	84.729	1.00	44.49	A C
ATOM	2590	CG1	VAL	A	335	64.650	133.304	85.948	1.00	45.61	A C
ATOM	2591	CG2	VAL	A	335	63.081	133.714	84.039	1.00	38.67	A C
ATOM	2592	C	VAL	A	335	65.525	136.104	85.816	1.00	48.02	A C
ATOM	2593	O	VAL	A	335	66.618	135.993	85.263	1.00	50.07	A O
ATOM	2594	N	VAL	A	336	65.379	136.641	87.021	1.00	48.52	A N
ATOM	2595	CA	VAL	A	336	66.507	137.122	87.800	1.00	48.28	A C
ATOM	2596	CB	VAL	A	336	66.117	138.361	88.610	1.00	47.72	A C
ATOM	2597	CG1	VAL	A	336	67.234	138.731	89.567	1.00	46.98	A C
ATOM	2598	CG2	VAL	A	336	65.810	139.513	87.670	1.00	46.73	A C
ATOM	2599	C	VAL	A	336	66.981	136.038	88.763	1.00	50.86	A C
ATOM	2600	O	VAL	A	336	66.224	135.573	89.619	1.00	52.30	A O
ATOM	2601	N	GLY	A	337	68.235	135.631	88.609	1.00	51.74	A N
ATOM	2602	CA	GLY	A	337	68.791	134.614	89.477	1.00	52.95	A C
ATOM	2603	C	GLY	A	337	69.846	135.212	90.385	1.00	54.70	A C
ATOM	2604	O	GLY	A	337	70.870	135.699	89.905	1.00	54.43	A O
ATOM	2605	N	ILE	A	338	69.598	135.187	91.692	1.00	56.43	A N
ATOM	2606	CA	ILE	A	338	70.542	135.734	92.655	1.00	58.58	A C
ATOM	2607	CB	ILE	A	338	69.818	136.467	93.796	1.00	59.10	A C
ATOM	2608	CG2	ILE	A	338	70.828	137.282	94.598	1.00	58.37	A C
ATOM	2609	CG1	ILE	A	338	68.734	137.386	93.227	1.00	59.14	A C
ATOM	2610	CD1	ILE	A	338	67.986	138.186	94.290	1.00	57.57	A C
ATOM	2611	C	ILE	A	338	71.398	134.628	93.262	1.00	59.93	A C
ATOM	2612	O	ILE	A	338	70.923	133.839	94.076	1.00	61.42	A O
ATOM	2613	N	GLY	A	339	72.664	134.571	92.865	1.00	61.13	A N
ATOM	2614	CA	GLY	A	339	73.548	133.546	93.389	1.00	62.48	A C
ATOM	2615	C	GLY	A	339	73.925	132.476	92.378	1.00	62.93	A C
ATOM	2616	O	GLY	A	339	73.067	131.872	91.742	1.00	62.69	A O
ATOM	2617	N	SER	A	340	75.225	132.240	92.249	1.00	63.32	A N
ATOM	2618	CA	SER	A	340	75.765	131.256	91.323	1.00	64.75	A C
ATOM	2619	CB	SER	A	340	77.217	130.930	91.699	1.00	66.19	A C
ATOM	2620	OG	SER	A	340	77.963	132.112	91.961	1.00	69.15	A O

FIGURE 11-53

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ATOM   2621  C   SER A 340      74.969 129.954  91.264  1.00 64.69      A    C
ATOM   2622  O   SER A 340      74.736 129.416  90.182  1.00 64.46      A    O
ATOM   2623  N   ASP A 341      74.555 129.443  92.420  1.00 64.70      A    N
ATOM   2624  CA  ASP A 341      73.819 128.181  92.462  1.00 63.69      A    C
ATOM   2625  CB  ASP A 341      73.771 127.642  93.894  1.00 67.31      A    C
ATOM   2626  CG  ASP A 341      75.139 127.234  94.406  1.00 70.14      A    C
ATOM   2627  OD1 ASP A 341      75.926 128.133  94.779  1.00 72.20      A    O
ATOM   2628  OD2 ASP A 341      75.431 126.014  94.420  1.00 70.95      A    O
ATOM   2629  C   ASP A 341      72.412 128.247  91.898  1.00 61.00      A    C
ATOM   2630  O   ASP A 341      71.700 127.251  91.851  1.00 60.31      A    O
ATOM   2631  N   THR A 342      72.018 129.424  91.447  1.00 59.71      A    N
ATOM   2632  CA  THR A 342      70.688 129.611  90.899  1.00 58.26      A    C
ATOM   2633  CB  THR A 342      70.162 130.995  91.351  1.00 59.30      A    C
ATOM   2634  OG1 THR A 342      68.763 130.909  91.649  1.00 64.24      A    O
ATOM   2635  CG2 THR A 342      70.406 132.037  90.288  1.00 59.08      A    C
ATOM   2636  C   THR A 342      70.732 129.487  89.360  1.00 56.86      A    C
ATOM   2637  O   THR A 342      69.703 129.511  88.677  1.00 54.13      A    O
ATOM   2638  N   ASN A 343      71.945 129.314  88.840  1.00 55.31      A    N
ATOM   2639  CA  ASN A 343      72.204 129.216  87.410  1.00 53.54      A    C
ATOM   2640  CB  ASN A 343      73.671 128.845  87.185  1.00 52.30      A    C
ATOM   2641  CG  ASN A 343      74.164 129.236  85.809  1.00 52.09      A    C
ATOM   2642  OD1 ASN A 343      73.798 130.289  85.290  1.00 52.28      A    O
ATOM   2643  ND2 ASN A 343      75.017 128.403  85.219  1.00 50.14      A    N
ATOM   2644  C   ASN A 343      71.310 128.231  86.679  1.00 53.47      A    C
ATOM   2645  O   ASN A 343      70.569 128.608  85.774  1.00 54.07      A    O
ATOM   2646  N   VAL A 344      71.385 126.966  87.074  1.00 52.53      A    N
ATOM   2647  CA  VAL A 344      70.591 125.920  86.447  1.00 49.67      A    C
ATOM   2648  CB  VAL A 344      70.822 124.566  87.134  1.00 49.15      A    C
ATOM   2649  CG1 VAL A 344      70.064 123.479  86.403  1.00 48.68      A    C
ATOM   2650  CG2 VAL A 344      72.302 124.249  87.152  1.00 49.59      A    C
ATOM   2651  C   VAL A 344      69.098 126.217  86.449  1.00 48.48      A    C
ATOM   2652  O   VAL A 344      68.455 126.165  85.404  1.00 48.01      A    O
ATOM   2653  N   ALA A 345      68.544 126.520  87.618  1.00 46.52      A    N
ATOM   2654  CA  ALA A 345      67.119 126.808  87.718  1.00 46.04      A    C
ATOM   2655  CB  ALA A 345      66.738 127.106  89.169  1.00 46.34      A    C
ATOM   2656  C   ALA A 345      66.735 127.979  86.825  1.00 45.48      A    C
ATOM   2657  O   ALA A 345      65.667 127.977  86.207  1.00 44.50      A    O
ATOM   2658  N   ALA A 346      67.611 128.981  86.765  1.00 46.08      A    N
ATOM   2659  CA  ALA A 346      67.374 130.162  85.941  1.00 45.01      A    C
ATOM   2660  CB  ALA A 346      68.561 131.105  86.031  1.00 46.09      A    C
ATOM   2661  C   ALA A 346      67.139 129.746  84.487  1.00 45.32      A    C
ATOM   2662  O   ALA A 346      66.221 130.243  83.832  1.00 46.54      A    O
ATOM   2663  N   LEU A 347      67.972 128.838  83.988  1.00 44.22      A    N
ATOM   2664  CA  LEU A 347      67.831 128.345  82.626  1.00 44.28      A    C
ATOM   2665  CB  LEU A 347      69.026 127.469  82.255  1.00 41.69      A    C
ATOM   2666  CG  LEU A 347      68.927 126.833  80.866  1.00 41.33      A    C
ATOM   2667  CD1 LEU A 347      69.098 127.915  79.805  1.00 41.15      A    C
ATOM   2668  CD2 LEU A 347      69.991 125.784  80.692  1.00 38.06      A    C
ATOM   2669  C   LEU A 347      66.544 127.518  82.483  1.00 46.87      A    C
ATOM   2670  O   LEU A 347      65.812 127.657  81.497  1.00 47.27      A    O
ATOM   2671  N   GLN A 348      66.265 126.660  83.464  1.00 46.53      A    N
ATOM   2672  CA  GLN A 348      65.071 125.820  83.397  1.00 49.09      A    C
ATOM   2673  CB  GLN A 348      64.956 124.918  84.630  1.00 51.30      A    C
ATOM   2674  CG  GLN A 348      66.225 124.177  84.990  1.00 56.51      A    C
ATOM   2675  CD  GLN A 348      66.006 123.150  86.084  1.00 56.11      A    C
ATOM   2676  OE1 GLN A 348      65.276 122.180  85.895  1.00 59.37      A    O
ATOM   2677  NE2 GLN A 348      66.637 123.360  87.234  1.00 57.24      A    N
ATOM   2678  C   GLN A 348      63.851 126.716  83.333  1.00 47.37      A    C
ATOM   2679  O   GLN A 348      62.910 126.469  82.578  1.00 46.14      A    O
ATOM   2680  N   LEU A 349      63.889 127.762  84.141  1.00 46.11      A    N
ATOM   2681  CA  LEU A 349      62.803 128.722  84.221  1.00 48.09      A    C
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FIGURE 11-54

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ATOM   2682  CB  LEU A 349      63.116 129.719  85.341  1.00 48.35      A    C
ATOM   2683  CG  LEU A 349      62.107 130.003  86.460  1.00 47.66      A    C
ATOM   2684  CD1 LEU A 349      61.315 128.757  86.813  1.00 44.02      A    C
ATOM   2685  CD2 LEU A 349      62.873 130.539  87.676  1.00 45.02      A    C
ATOM   2686  C   LEU A 349      62.558 129.455  82.889  1.00 48.67      A    C
ATOM   2687  O   LEU A 349      61.417 129.534  82.427  1.00 47.19      A    O
ATOM   2688  N   VAL A 350      63.618 129.972  82.266  1.00 47.89      A    N
ATOM   2689  CA  VAL A 350      63.451 130.691  81.009  1.00 48.32      A    C
ATOM   2690  CB  VAL A 350      64.731 131.476  80.598  1.00 49.72      A    C
ATOM   2691  CG1 VAL A 350      65.852 130.526  80.209  1.00 48.81      A    C
ATOM   2692  CG2 VAL A 350      64.415 132.386  79.436  1.00 51.58      A    C
ATOM   2693  C   VAL A 350      63.051 129.771  79.870  1.00 49.16      A    C
ATOM   2694  O   VAL A 350      62.298 130.173  78.987  1.00 48.96      A    O
ATOM   2695  N   GLN A 351      63.536 128.535  79.869  1.00 49.45      A    N
ATOM   2696  CA  GLN A 351      63.149 127.635  78.789  1.00 51.84      A    C
ATOM   2697  CB  GLN A 351      64.042 126.389  78.746  1.00 50.72      A    C
ATOM   2698  CG  GLN A 351      65.402 126.656  78.116  1.00 49.94      A    C
ATOM   2699  CD  GLN A 351      65.290 127.496  76.845  1.00 49.54      A    C
ATOM   2700  OE1 GLN A 351      64.691 127.076  75.849  1.00 47.25      A    O
ATOM   2701  NE2 GLN A 351      65.855 128.697  76.885  1.00 47.61      A    N
ATOM   2702  C   GLN A 351      61.682 127.235  78.905  1.00 53.61      A    C
ATOM   2703  O   GLN A 351      60.978 127.153  77.898  1.00 56.84      A    O
ATOM   2704  N   SER A 352      61.219 126.996  80.129  1.00 53.40      A    N
ATOM   2705  CA  SER A 352      59.827 126.628  80.349  1.00 53.23      A    C
ATOM   2706  CB  SER A 352      59.569 126.347  81.833  1.00 54.40      A    C
ATOM   2707  OG  SER A 352      60.073 125.072  82.202  1.00 57.62      A    O
ATOM   2708  C   SER A 352      58.919 127.751  79.872  1.00 52.89      A    C
ATOM   2709  O   SER A 352      57.911 127.502  79.214  1.00 53.27      A    O
ATOM   2710  N   ILE A 353      59.278 128.988  80.206  1.00 53.02      A    N
ATOM   2711  CA  ILE A 353      58.489 130.140  79.789  1.00 53.10      A    C
ATOM   2712  CB  ILE A 353      59.078 131.461  80.342  1.00 50.86      A    C
ATOM   2713  CG2 ILE A 353      58.346 132.655  79.746  1.00 49.42      A    C
ATOM   2714  CG1 ILE A 353      58.956 131.478  81.868  1.00 50.88      A    C
ATOM   2715  CD1 ILE A 353      59.528 132.716  82.536  1.00 46.87      A    C
ATOM   2716  C   ILE A 353      58.454 130.181  78.262  1.00 54.12      A    C
ATOM   2717  O   ILE A 353      57.405 130.418  77.660  1.00 54.39      A    O
ATOM   2718  N   ARG A 354      59.599 129.935  77.635  1.00 54.49      A    N
ATOM   2719  CA  ARG A 354      59.658 129.929  76.182  1.00 54.62      A    C
ATOM   2720  CB  ARG A 354      61.108 129.851  75.711  1.00 52.11      A    C
ATOM   2721  CG  ARG A 354      61.865 131.162  75.881  1.00 50.93      A    C
ATOM   2722  CD  ARG A 354      63.352 130.993  75.664  1.00 45.70      A    C
ATOM   2723  NE  ARG A 354      64.069 132.252  75.827  1.00 46.40      A    N
ATOM   2724  CZ  ARG A 354      65.378 132.342  76.053  1.00 45.16      A    C
ATOM   2725  NH1 ARG A 354      66.116 131.246  76.154  1.00 42.38      A    N
ATOM   2726  NH2 ARG A 354      65.960 133.529  76.153  1.00 45.77      A    N
ATOM   2727  C   ARG A 354      58.867 128.740  75.658  1.00 56.76      A    C
ATOM   2728  O   ARG A 354      58.335 128.777  74.552  1.00 56.97      A    O
ATOM   2729  N   ASN A 355      58.780 127.688  76.464  1.00 59.07      A    N
ATOM   2730  CA  ASN A 355      58.043 126.497  76.071  1.00 61.26      A    C
ATOM   2731  CB  ASN A 355      58.329 125.345  77.034  1.00 64.80      A    C
ATOM   2732  CG  ASN A 355      57.842 124.008  76.495  1.00 69.75      A    C
ATOM   2733  OD1 ASN A 355      58.341 123.527  75.472  1.00 72.24      A    O
ATOM   2734  ND2 ASN A 355      56.859 123.406  77.171  1.00 68.76      A    N
ATOM   2735  C   ASN A 355      56.535 126.761  76.030  1.00 61.29      A    C
ATOM   2736  O   ASN A 355      55.796 126.079  75.316  1.00 60.42      A    O
ATOM   2737  N   PHE A 356      56.078 127.740  76.804  1.00 60.98      A    N
ATOM   2738  CA  PHE A 356      54.662 128.080  76.821  1.00 62.03      A    C
ATOM   2739  CB  PHE A 356      54.212 128.492  78.228  1.00 63.50      A    C
ATOM   2740  CG  PHE A 356      53.920 127.329  79.133  1.00 65.74      A    C
ATOM   2741  CD1 PHE A 356      54.952 126.533  79.626  1.00 66.97      A    C
ATOM   2742  CD2 PHE A 356      52.609 127.001  79.460  1.00 67.13      A    C
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FIGURE 11-55

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ATOM   2743  CE1 PHE A 356      54.682 125.423  80.430  1.00 66.68      A    C
ATOM   2744  CE2 PHE A 356      52.325 125.894  80.263  1.00 67.26      A    C
ATOM   2745  CZ  PHE A 356      53.364 125.104  80.748  1.00 67.64      A    C
ATOM   2746  C   PHE A 356      54.345 129.195  75.831  1.00 62.74      A    C
ATOM   2747  O   PHE A 356      53.339 129.897  75.979  1.00 64.04      A    O
ATOM   2748  N   GLY A 357      55.211 129.363  74.833  1.00 61.84      A    N
ATOM   2749  CA  GLY A 357      54.993 130.380  73.815  1.00 60.87      A    C
ATOM   2750  C   GLY A 357      55.451 131.800  74.117  1.00 60.25      A    C
ATOM   2751  O   GLY A 357      55.687 132.585  73.193  1.00 60.47      A    O
ATOM   2752  N   PHE A 358      55.584 132.139  75.396  1.00 57.84      A    N
ATOM   2753  CA  PHE A 358      56.009 133.476  75.789  1.00 55.46      A    C
ATOM   2754  CB  PHE A 358      55.727 133.686  77.267  1.00 56.07      A    C
ATOM   2755  CG  PHE A 358      54.307 133.410  77.656  1.00 56.93      A    C
ATOM   2756  CD1 PHE A 358      53.895 132.119  77.962  1.00 56.76      A    C
ATOM   2757  CD2 PHE A 358      53.381 134.449  77.734  1.00 58.48      A    C
ATOM   2758  CE1 PHE A 358      52.579 131.863  78.348  1.00 58.47      A    C
ATOM   2759  CE2 PHE A 358      52.061 134.204  78.117  1.00 58.87      A    C
ATOM   2760  CZ  PHE A 358      51.661 132.911  78.425  1.00 57.49      A    C
ATOM   2761  C   PHE A 358      57.483 133.786  75.504  1.00 53.58      A    C
ATOM   2762  O   PHE A 358      58.253 132.912  75.118  1.00 54.47      A    O
ATOM   2763  N   SER A 359      57.860 135.049  75.685  1.00 51.32      A    N
ATOM   2764  CA  SER A 359      59.233 135.489  75.458  1.00 48.53      A    C
ATOM   2765  CB  SER A 359      59.249 136.804  74.687  1.00 48.54      A    C
ATOM   2766  OG  SER A 359      58.700 137.844  75.481  1.00 49.78      A    O
ATOM   2767  C   SER A 359      59.922 135.696  76.803  1.00 46.80      A    C
ATOM   2768  O   SER A 359      59.305 136.161  77.767  1.00 44.80      A    O
ATOM   2769  N   ALA A 360      61.207 135.375  76.862  1.00 45.26      A    N
ATOM   2770  CA  ALA A 360      61.933 135.519  78.107  1.00 45.01      A    C
ATOM   2771  CB  ALA A 360      61.694 134.287  78.978  1.00 44.59      A    C
ATOM   2772  C   ALA A 360      63.426 135.732  77.937  1.00 44.26      A    C
ATOM   2773  O   ALA A 360      63.997 135.506  76.867  1.00 42.40      A    O
ATOM   2774  N   ASP A 361      64.048 136.167  79.023  1.00 42.32      A    N
ATOM   2775  CA  ASP A 361      65.479 136.380  79.052  1.00 41.91      A    C
ATOM   2776  CB  ASP A 361      65.842 137.755  78.474  1.00 42.19      A    C
ATOM   2777  CG  ASP A 361      67.322 137.866  78.104  1.00 45.99      A    C
ATOM   2778  OD1 ASP A 361      67.805 139.005  77.916  1.00 50.55      A    O
ATOM   2779  OD2 ASP A 361      68.001 136.815  77.990  1.00 46.77      A    O
ATOM   2780  C   ASP A 361      65.953 136.282  80.502  1.00 40.26      A    C
ATOM   2781  O   ASP A 361      65.161 136.361  81.446  1.00 39.14      A    O
ATOM   2782  N   ARG A 362      67.254 136.104  80.665  1.00 40.29      A    N
ATOM   2783  CA  ARG A 362      67.851 136.013  81.980  1.00 39.94      A    C
ATOM   2784  CB  ARG A 362      67.846 134.565  82.459  1.00 38.50      A    C
ATOM   2785  CG  ARG A 362      68.506 133.610  81.489  1.00 40.47      A    C
ATOM   2786  CD  ARG A 362      69.051 132.384  82.201  1.00 42.43      A    C
ATOM   2787  NE  ARG A 362      70.098 132.739  83.167  1.00 42.07      A    N
ATOM   2788  CZ  ARG A 362      70.918 131.854  83.726  1.00 39.97      A    C
ATOM   2789  NH1 ARG A 362      70.811 130.570  83.419  1.00 39.00      A    N
ATOM   2790  NH2 ARG A 362      71.852 132.249  84.574  1.00 37.17      A    N
ATOM   2791  C   ARG A 362      69.284 136.502  81.853  1.00 41.80      A    C
ATOM   2792  O   ARG A 362      69.779 136.715  80.736  1.00 42.18      A    O
ATOM   2793  N   ASP A 363      69.948 136.681  82.990  1.00 39.74      A    N
ATOM   2794  CA  ASP A 363      71.330 137.114  82.979  1.00 39.41      A    C
ATOM   2795  CB  ASP A 363      71.668 137.848  84.271  1.00 40.75      A    C
ATOM   2796  CG  ASP A 363      72.883 138.725  84.119  1.00 44.48      A    C
ATOM   2797  OD1 ASP A 363      74.014 138.251  84.354  1.00 39.07      A    O
ATOM   2798  OD2 ASP A 363      72.695 139.897  83.719  1.00 52.59      A    O
ATOM   2799  C   ASP A 363      72.257 135.906  82.782  1.00 39.92      A    C
ATOM   2800  O   ASP A 363      71.904 134.775  83.114  1.00 40.49      A    O
ATOM   2801  N   TYR A 364      73.428 136.146  82.203  1.00 39.89      A    N
ATOM   2802  CA  TYR A 364      74.386 135.082  81.940  1.00 41.28      A    C
ATOM   2803  CB  TYR A 364      74.371 134.701  80.457  1.00 39.18      A    C
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FIGURE 11-56

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ATOM   2804  CG  TYR A 364      73.197 133.835  80.075  1.00 40.90      A    C
ATOM   2805  CD1 TYR A 364      72.250 134.269  79.146  1.00 39.62      A    C
ATOM   2806  CE1 TYR A 364      71.162 133.471  78.805  1.00 39.88      A    C
ATOM   2807  CD2 TYR A 364      73.026 132.581  80.655  1.00 38.81      A    C
ATOM   2808  CE2 TYR A 364      71.950 131.780  80.325  1.00 41.50      A    C
ATOM   2809  CZ  TYR A 364      71.017 132.221  79.400  1.00 41.93      A    C
ATOM   2810  OH  TYR A 364      69.960 131.394  79.069  1.00 38.31      A    O
ATOM   2811  C   TYR A 364      75.781 135.520  82.329  1.00 42.38      A    C
ATOM   2812  O   TYR A 364      76.741 134.769  82.174  1.00 40.90      A    O
ATOM   2813  N   MET A 365      75.869 136.743  82.841  1.00 44.68      A    N
ATOM   2814  CA  MET A 365      77.132 137.343  83.255  1.00 47.83      A    C
ATOM   2815  CB  MET A 365      77.190 138.791  82.763  1.00 45.49      A    C
ATOM   2816  CG  MET A 365      76.994 138.930  81.270  1.00 42.57      A    C
ATOM   2817  SD  MET A 365      78.204 137.929  80.383  1.00 46.39      A    S
ATOM   2818  CE  MET A 365      79.725 138.748  80.918  1.00 42.26      A    C
ATOM   2819  C   MET A 365      77.295 137.311  84.775  1.00 51.27      A    C
ATOM   2820  O   MET A 365      78.203 137.945  85.317  1.00 51.91      A    O
ATOM   2821  N   ASN A 366      76.403 136.578  85.444  1.00 53.99      A    N
ATOM   2822  CA  ASN A 366      76.410 136.434  86.899  1.00 56.62      A    C
ATOM   2823  CB  ASN A 366      77.518 135.452  87.323  1.00 59.67      A    C
ATOM   2824  CG  ASN A 366      77.403 135.018  88.785  1.00 61.76      A    C
ATOM   2825  OD1 ASN A 366      76.302 134.849  89.318  1.00 62.56      A    O
ATOM   2826  ND2 ASN A 366      78.545 134.818  89.431  1.00 62.93      A    N
ATOM   2827  C   ASN A 366      76.599 137.788  87.568  1.00 57.41      A    C
ATOM   2828  O   ASN A 366      77.516 137.988  88.361  1.00 56.53      A    O
ATOM   2829  N   ARG A 367      75.710 138.718  87.240  1.00 58.89      A    N
ATOM   2830  CA  ARG A 367      75.771 140.065  87.786  1.00 60.20      A    C
ATOM   2831  CB  ARG A 367      75.333 141.075  86.722  1.00 61.20      A    C
ATOM   2832  CG  ARG A 367      76.150 140.981  85.444  1.00 63.43      A    C
ATOM   2833  CD  ARG A 367      75.747 142.038  84.445  1.00 65.17      A    C
ATOM   2834  NE  ARG A 367      74.299 142.090  84.305  1.00 69.75      A    N
ATOM   2835  CZ  ARG A 367      73.663 142.716  83.321  1.00 72.12      A    C
ATOM   2836  NH1 ARG A 367      72.333 142.708  83.284  1.00 70.94      A    N
ATOM   2837  NH2 ARG A 367      74.357 143.336  82.369  1.00 73.82      A    N
ATOM   2838  C   ARG A 367      74.907 140.214  89.023  1.00 60.31      A    C
ATOM   2839  O   ARG A 367      74.043 139.376  89.290  1.00 59.81      A    O
ATOM   2840  N   LYS A 368      75.143 141.287  89.774  1.00 61.22      A    N
ATOM   2841  CA  LYS A 368      74.376 141.547  90.987  1.00 62.16      A    C
ATOM   2842  CB  LYS A 368      74.926 142.768  91.725  1.00 61.01      A    C
ATOM   2843  CG  LYS A 368      76.292 142.553  92.350  1.00 59.96      A    C
ATOM   2844  CD  LYS A 368      76.612 143.703  93.291  1.00 61.23      A    C
ATOM   2845  CE  LYS A 368      78.018 143.593  93.869  1.00 60.24      A    C
ATOM   2846  NZ  LYS A 368      78.275 144.703  94.836  1.00 59.17      A    N
ATOM   2847  C   LYS A 368      72.901 141.759  90.675  1.00 62.59      A    C
ATOM   2848  O   LYS A 368      72.544 142.273  89.616  1.00 63.08      A    O
ATOM   2849  N   PRO A 369      72.023 141.366  91.607  1.00 63.32      A    N
ATOM   2850  CD  PRO A 369      72.355 140.896  92.962  1.00 62.99      A    C
ATOM   2851  CA  PRO A 369      70.571 141.503  91.441  1.00 63.56      A    C
ATOM   2852  CB  PRO A 369      70.023 141.107  92.816  1.00 63.57      A    C
ATOM   2853  CG  PRO A 369      71.175 141.391  93.750  1.00 64.55      A    C
ATOM   2854  C   PRO A 369      70.109 142.886  90.990  1.00 63.51      A    C
ATOM   2855  O   PRO A 369      69.227 143.005  90.135  1.00 63.90      A    O
ATOM   2856  N   LYS A 370      70.707 143.926  91.560  1.00 63.51      A    N
ATOM   2857  CA  LYS A 370      70.363 145.302  91.202  1.00 63.84      A    C
ATOM   2858  CB  LYS A 370      71.261 146.278  91.982  1.00 65.59      A    C
ATOM   2859  CG  LYS A 370      70.992 147.764  91.724  1.00 68.21      A    C
ATOM   2860  CD  LYS A 370      69.597 148.182  92.178  1.00 69.71      A    C
ATOM   2861  CE  LYS A 370      69.363 149.690  92.013  1.00 70.99      A    C
ATOM   2862  NZ  LYS A 370      70.121 150.523  93.000  1.00 71.57      A    N
ATOM   2863  C   LYS A 370      70.531 145.526  89.690  1.00 61.80      A    C
ATOM   2864  O   LYS A 370      69.669 146.116  89.037  1.00 61.70      A    O
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FIGURE 11-57

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ATOM   2865  N   ALA A 371      71.641 145.047  89.140  1.00 59.20      A    N
ATOM   2866  CA  ALA A 371      71.910 145.202  87.717  1.00 58.19      A    C
ATOM   2867  CB  ALA A 371      73.315 144.722  87.401  1.00 55.80      A    C
ATOM   2868  C   ALA A 371      70.897 144.442  86.868  1.00 57.61      A    C
ATOM   2869  O   ALA A 371      70.444 144.937  85.832  1.00 58.05      A    O
ATOM   2870  N   GLN A 372      70.546 143.236  87.302  1.00 56.44      A    N
ATOM   2871  CA  GLN A 372      69.587 142.428  86.566  1.00 55.83      A    C
ATOM   2872  CB  GLN A 372      69.458 141.045  87.192  1.00 56.05      A    C
ATOM   2873  CG  GLN A 372      70.726 140.228  87.142  1.00 56.62      A    C
ATOM   2874  CD  GLN A 372      70.519 138.820  87.655  1.00 58.80      A    C
ATOM   2875  OE1 GLN A 372      69.673 138.073  87.144  1.00 57.69      A    O
ATOM   2876  NE2 GLN A 372      71.291 138.444  88.671  1.00 59.51      A    N
ATOM   2877  C   GLN A 372      68.216 143.086  86.511  1.00 56.53      A    C
ATOM   2878  O   GLN A 372      67.558 143.063  85.469  1.00 57.38      A    O
ATOM   2879  N   PHE A 373      67.769 143.661  87.623  1.00 55.36      A    N
ATOM   2880  CA  PHE A 373      66.472 144.318  87.613  1.00 56.51      A    C
ATOM   2881  CB  PHE A 373      66.080 144.795  89.014  1.00 55.71      A    C
ATOM   2882  CG  PHE A 373      65.674 143.680  89.936  1.00 56.13      A    C
ATOM   2883  CD1 PHE A 373      66.438 143.369  91.056  1.00 55.83      A    C
ATOM   2884  CD2 PHE A 373      64.534 142.925  89.671  1.00 55.74      A    C
ATOM   2885  CE1 PHE A 373      66.075 142.322  91.897  1.00 55.19      A    C
ATOM   2886  CE2 PHE A 373      64.163 141.880  90.503  1.00 54.69      A    C
ATOM   2887  CZ  PHE A 373      64.935 141.576  91.619  1.00 55.79      A    C
ATOM   2888  C   PHE A 373      66.542 145.489  86.649  1.00 57.66      A    C
ATOM   2889  O   PHE A 373      65.570 145.786  85.959  1.00 57.75      A    O
ATOM   2890  N   LYS A 374      67.699 146.146  86.594  1.00 58.93      A    N
ATOM   2891  CA  LYS A 374      67.876 147.267  85.682  1.00 60.37      A    C
ATOM   2892  CB  LYS A 374      69.277 147.872  85.812  1.00 63.59      A    C
ATOM   2893  CG  LYS A 374      69.477 148.754  87.040  1.00 67.78      A    C
ATOM   2894  CD  LYS A 374      70.771 149.560  86.924  1.00 72.23      A    C
ATOM   2895  CE  LYS A 374      70.874 150.629  88.010  1.00 74.35      A    C
ATOM   2896  NZ  LYS A 374      71.949 151.631  87.710  1.00 76.30      A    N
ATOM   2897  C   LYS A 374      67.674 146.771  84.263  1.00 59.79      A    C
ATOM   2898  O   LYS A 374      66.987 147.407  83.465  1.00 60.52      A    O
ATOM   2899  N   THR A 375      68.268 145.625  83.954  1.00 58.08      A    N
ATOM   2900  CA  THR A 375      68.143 145.048  82.625  1.00 58.48      A    C
ATOM   2901  CB  THR A 375      69.025 143.789  82.476  1.00 57.57      A    C
ATOM   2902  OG1 THR A 375      70.390 144.121  82.757  1.00 58.66      A    O
ATOM   2903  CG2 THR A 375      68.930 143.237  81.065  1.00 55.34      A    C
ATOM   2904  C   THR A 375      66.693 144.667  82.353  1.00 58.68      A    C
ATOM   2905  O   THR A 375      66.180 144.878  81.256  1.00 59.45      A    O
ATOM   2906  N   ALA A 376      66.033 144.104  83.357  1.00 59.16      A    N
ATOM   2907  CA  ALA A 376      64.641 143.690  83.213  1.00 60.05      A    C
ATOM   2908  CB  ALA A 376      64.155 143.041  84.497  1.00 59.51      A    C
ATOM   2909  C   ALA A 376      63.748 144.874  82.861  1.00 61.02      A    C
ATOM   2910  O   ALA A 376      62.972 144.815  81.903  1.00 60.48      A    O
ATOM   2911  N   ASP A 377      63.855 145.942  83.649  1.00 61.57      A    N
ATOM   2912  CA  ASP A 377      63.061 147.139  83.421  1.00 63.48      A    C
ATOM   2913  CB  ASP A 377      63.314 148.171  84.524  1.00 66.43      A    C
ATOM   2914  CG  ASP A 377      62.529 147.875  85.796  1.00 69.11      A    C
ATOM   2915  OD1 ASP A 377      62.733 148.596  86.793  1.00 69.81      A    O
ATOM   2916  OD2 ASP A 377      61.706 146.931  85.800  1.00 71.04      A    O
ATOM   2917  C   ASP A 377      63.414 147.731  82.071  1.00 63.24      A    C
ATOM   2918  O   ASP A 377      62.529 148.085  81.290  1.00 63.25      A    O
ATOM   2919  N   LYS A 378      64.712 147.824  81.798  1.00 62.77      A    N
ATOM   2920  CA  LYS A 378      65.194 148.365  80.534  1.00 63.19      A    C
ATOM   2921  CB  LYS A 378      66.719 148.261  80.461  1.00 66.13      A    C
ATOM   2922  CG  LYS A 378      67.325 148.700  79.130  1.00 68.82      A    C
ATOM   2923  CD  LYS A 378      68.812 148.349  79.056  1.00 71.01      A    C
ATOM   2924  CE  LYS A 378      69.383 148.621  77.670  1.00 73.39      A    C
ATOM   2925  NZ  LYS A 378      69.290 150.063  77.280  1.00 75.28      A    N
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FIGURE 11-58

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ATOM   2926  C   LYS A 378      64.575 147.627  79.353  1.00 62.22      A    C
ATOM   2927  O   LYS A 378      64.257 148.234  78.340  1.00 62.02      A    O
ATOM   2928  N   LEU A 379      64.405 146.315  79.484  1.00 61.78      A    N
ATOM   2929  CA  LEU A 379      63.821 145.526  78.410  1.00 60.34      A    C
ATOM   2930  CB  LEU A 379      64.393 144.109  78.434  1.00 59.96      A    C
ATOM   2931  CG  LEU A 379      65.899 143.943  78.203  1.00 61.44      A    C
ATOM   2932  CD1 LEU A 379      66.277 142.472  78.345  1.00 58.02      A    C
ATOM   2933  CD2 LEU A 379      66.277 144.468  76.822  1.00 59.99      A    C
ATOM   2934  C   LEU A 379      62.292 145.490  78.494  1.00 60.37      A    C
ATOM   2935  O   LEU A 379      61.631 144.768  77.745  1.00 59.55      A    O
ATOM   2936  N   GLN A 380      61.736 146.277  79.410  1.00 60.24      A    N
ATOM   2937  CA  GLN A 380      60.285 146.370  79.584  1.00 60.96      A    C
ATOM   2938  CB  GLN A 380      59.638 147.006  78.347  1.00 63.37      A    C
ATOM   2939  CG  GLN A 380      59.940 148.487  78.150  1.00 67.22      A    C
ATOM   2940  CD  GLN A 380      59.210 149.079  76.946  1.00 70.69      A    C
ATOM   2941  OE1 GLN A 380      59.303 150.284  76.678  1.00 71.11      A    O
ATOM   2942  NE2 GLN A 380      58.480 148.234  76.213  1.00 69.40      A    N
ATOM   2943  C   GLN A 380      59.581 145.053  79.869  1.00 59.26      A    C
ATOM   2944  O   GLN A 380      58.415 144.883  79.505  1.00 58.39      A    O
ATOM   2945  N   ALA A 381      60.277 144.125  80.516  1.00 58.00      A    N
ATOM   2946  CA  ALA A 381      59.675 142.835  80.838  1.00 57.48      A    C
ATOM   2947  CB  ALA A 381      60.619 142.016  81.706  1.00 56.15      A    C
ATOM   2948  C   ALA A 381      58.353 143.059  81.565  1.00 57.44      A    C
ATOM   2949  O   ALA A 381      58.259 143.909  82.453  1.00 56.03      A    O
ATOM   2950  N   LYS A 382      57.330 142.309  81.174  1.00 58.12      A    N
ATOM   2951  CA  LYS A 382      56.021 142.436  81.801  1.00 59.32      A    C
ATOM   2952  CB  LYS A 382      54.946 141.779  80.935  1.00 61.24      A    C
ATOM   2953  CG  LYS A 382      54.778 142.416  79.572  1.00 63.50      A    C
ATOM   2954  CD  LYS A 382      53.734 141.686  78.753  1.00 65.85      A    C
ATOM   2955  CE  LYS A 382      53.661 142.252  77.343  1.00 67.95      A    C
ATOM   2956  NZ  LYS A 382      52.600 141.572  76.539  1.00 70.41      A    N
ATOM   2957  C   LYS A 382      56.059 141.767  83.164  1.00 59.22      A    C
ATOM   2958  O   LYS A 382      55.496 142.272  84.138  1.00 60.58      A    O
ATOM   2959  N   LEU A 383      56.727 140.621  83.220  1.00 57.72      A    N
ATOM   2960  CA  LEU A 383      56.862 139.872  84.460  1.00 55.78      A    C
ATOM   2961  CB  LEU A 383      56.218 138.493  84.322  1.00 55.52      A    C
ATOM   2962  CG  LEU A 383      54.705 138.429  84.147  1.00 54.82      A    C
ATOM   2963  CD1 LEU A 383      54.314 137.043  83.680  1.00 54.81      A    C
ATOM   2964  CD2 LEU A 383      54.030 138.781  85.461  1.00 55.62      A    C
ATOM   2965  C   LEU A 383      58.340 139.703  84.780  1.00 55.01      A    C
ATOM   2966  O   LEU A 383      59.178 139.618  83.885  1.00 53.89      A    O
ATOM   2967  N   VAL A 384      58.651 139.657  86.065  1.00 55.23      A    N
ATOM   2968  CA  VAL A 384      60.019 139.485  86.518  1.00 55.81      A    C
ATOM   2969  CB  VAL A 384      60.596 140.788  87.123  1.00 56.47      A    C
ATOM   2970  CG1 VAL A 384      61.982 140.532  87.696  1.00 56.09      A    C
ATOM   2971  CG2 VAL A 384      60.678 141.859  86.059  1.00 56.82      A    C
ATOM   2972  C   VAL A 384      59.991 138.417  87.589  1.00 55.67      A    C
ATOM   2973  O   VAL A 384      59.368 138.591  88.635  1.00 56.12      A    O
ATOM   2974  N   LEU A 385      60.651 137.303  87.307  1.00 56.07      A    N
ATOM   2975  CA  LEU A 385      60.727 136.196  88.241  1.00 56.33      A    C
ATOM   2976  CB  LEU A 385      60.577 134.866  87.493  1.00 54.39      A    C
ATOM   2977  CG  LEU A 385      59.217 134.600  86.834  1.00 55.24      A    C
ATOM   2978  CD1 LEU A 385      59.068 135.454  85.586  1.00 53.00      A    C
ATOM   2979  CD2 LEU A 385      59.106 133.123  86.476  1.00 52.41      A    C
ATOM   2980  C   LEU A 385      62.078 136.252  88.956  1.00 56.87      A    C
ATOM   2981  O   LEU A 385      63.127 136.339  88.312  1.00 57.64      A    O
ATOM   2982  N   THR A 386      62.057 136.214  90.283  1.00 56.55      A    N
ATOM   2983  CA  THR A 386      63.303 136.257  91.042  1.00 57.18      A    C
ATOM   2984  CB  THR A 386      63.336 137.422  92.039  1.00 57.51      A    C
ATOM   2985  OG1 THR A 386      62.894 138.621  91.398  1.00 59.82      A    O
ATOM   2986  CG2 THR A 386      64.749 137.617  92.567  1.00 56.97      A    C
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FIGURE 11-59

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ATOM   2987  C   THR A 386      63.482 134.993  91.856  1.00 57.32      A    C
ATOM   2988  O   THR A 386      62.560 134.555  92.549  1.00 56.52      A    O
ATOM   2989  N   ILE A 387      64.671 134.410  91.773  1.00 57.32      A    N
ATOM   2990  CA  ILE A 387      64.962 133.212  92.532  1.00 58.57      A    C
ATOM   2991  CB  ILE A 387      64.925 131.952  91.652  1.00 58.86      A    C
ATOM   2992  CG2 ILE A 387      63.516 131.757  91.106  1.00 60.29      A    C
ATOM   2993  CG1 ILE A 387      65.949 132.064  90.523  1.00 58.31      A    C
ATOM   2994  CD1 ILE A 387      66.076 130.808  89.689  1.00 58.98      A    C
ATOM   2995  C   ILE A 387      66.315 133.298  93.217  1.00 59.69      A    C
ATOM   2996  O   ILE A 387      67.353 133.349  92.562  1.00 56.73      A    O
ATOM   2997  N   GLY A 388      66.283 133.332  94.547  1.00 62.16      A    N
ATOM   2998  CA  GLY A 388      67.503 133.389  95.329  1.00 65.89      A    C
ATOM   2999  C   GLY A 388      67.792 132.014  95.904  1.00 68.91      A    C
ATOM   3000  O   GLY A 388      67.018 131.076  95.692  1.00 67.08      A    O
ATOM   3001  N   GLU A 389      68.907 131.883  96.622  1.00 72.33      A    N
ATOM   3002  CA  GLU A 389      69.275 130.606  97.228  1.00 75.43      A    C
ATOM   3003  CB  GLU A 389      70.553 130.755  98.064  1.00 77.78      A    C
ATOM   3004  CG  GLU A 389      71.696 129.807  97.680  1.00 81.25      A    C
ATOM   3005  CD  GLU A 389      72.742 130.462  96.781  1.00 83.64      A    C
ATOM   3006  OE1 GLU A 389      73.146 131.611  97.078  1.00 83.36      A    O
ATOM   3007  OE2 GLU A 389      73.172 129.825  95.790  1.00 84.64      A    O
ATOM   3008  C   GLU A 389      68.126 130.150  98.127  1.00 75.44      A    C
ATOM   3009  O   GLU A 389      67.792 128.965  98.183  1.00 75.30      A    O
ATOM   3010  N   ASN A 390      67.523 131.110  98.823  1.00 75.38      A    N
ATOM   3011  CA  ASN A 390      66.411 130.830  99.721  1.00 75.38      A    C
ATOM   3012  CB  ASN A 390      66.115 132.062 100.596  1.00 78.10      A    C
ATOM   3013  CG  ASN A 390      66.549 133.377  99.942  1.00 81.24      A    C
ATOM   3014  OD1 ASN A 390      67.685 133.509  99.466  1.00 81.80      A    O
ATOM   3015  ND2 ASN A 390      65.649 134.360  99.933  1.00 81.82      A    N
ATOM   3016  C   ASN A 390      65.157 130.367  98.974  1.00 73.71      A    C
ATOM   3017  O   ASN A 390      64.459 129.464  99.435  1.00 74.10      A    O
ATOM   3018  N   GLU A 391      64.873 130.970  97.822  1.00 72.07      A    N
ATOM   3019  CA  GLU A 391      63.710 130.568  97.033  1.00 69.69      A    C
ATOM   3020  CB  GLU A 391      63.549 131.454  95.797  1.00 69.00      A    C
ATOM   3021  CG  GLU A 391      63.036 132.870  96.059  1.00 68.48      A    C
ATOM   3022  CD  GLU A 391      63.941 133.679  96.968  1.00 67.65      A    C
ATOM   3023  OE1 GLU A 391      65.149 133.372  97.042  1.00 67.16      A    O
ATOM   3024  OE2 GLU A 391      63.446 134.635  97.598  1.00 67.38      A    O
ATOM   3025  C   GLU A 391      63.904 129.124  96.589  1.00 69.36      A    C
ATOM   3026  O   GLU A 391      62.974 128.326  96.610  1.00 69.08      A    O
ATOM   3027  N   LEU A 392      65.123 128.791  96.185  1.00 69.92      A    N
ATOM   3028  CA  LEU A 392      65.418 127.436  95.748  1.00 71.08      A    C
ATOM   3029  CB  LEU A 392      66.872 127.319  95.296  1.00 72.40      A    C
ATOM   3030  CG  LEU A 392      67.205 127.954  93.948  1.00 72.55      A    C
ATOM   3031  CD1 LEU A 392      68.622 127.575  93.573  1.00 73.84      A    C
ATOM   3032  CD2 LEU A 392      66.227 127.469  92.886  1.00 72.51      A    C
ATOM   3033  C   LEU A 392      65.146 126.421  96.847  1.00 71.49      A    C
ATOM   3034  O   LEU A 392      64.473 125.417  96.610  1.00 71.23      A    O
ATOM   3035  N   ASN A 393      65.681 126.676  98.042  1.00 71.79      A    N
ATOM   3036  CA  ASN A 393      65.468 125.785  99.183  1.00 71.71      A    C
ATOM   3037  CB  ASN A 393      65.686 126.521 100.513  1.00 72.37      A    C
ATOM   3038  CG  ASN A 393      67.117 126.986 100.715  1.00 72.56      A    C
ATOM   3039  OD1 ASN A 393      68.061 126.196 100.650  1.00 73.26      A    O
ATOM   3040  ND2 ASN A 393      67.282 128.279 100.983  1.00 72.63      A    N
ATOM   3041  C   ASN A 393      64.021 125.298  99.155  1.00 71.69      A    C
ATOM   3042  O   ASN A 393      63.754 124.093  99.083  1.00 71.70      A    O
ATOM   3043  N   GLU A 394      63.097 126.258  99.198  1.00 70.36      A    N
ATOM   3044  CA  GLU A 394      61.673 125.961  99.200  1.00 69.08      A    C
ATOM   3045  CB  GLU A 394      60.897 127.109  99.852  1.00 70.11      A    C
ATOM   3046  CG  GLU A 394      59.429 126.768 100.090  1.00 73.61      A    C
ATOM   3047  CD  GLU A 394      58.612 127.932 100.610  1.00 74.30      A    C
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FIGURE 11-60

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ATOM   3048  OE1 GLU A 394      57.375 127.766 100.726  1.00 74.30      A    O
ATOM   3049  OE2 GLU A 394      59.200 129.000 100.904  1.00 74.64      A    O
ATOM   3050  C   GLU A 394      61.088 125.678  97.816  1.00 67.39      A    C
ATOM   3051  O   GLU A 394      59.869 125.540  97.672  1.00 66.42      A    O
ATOM   3052  N   GLY A 395      61.947 125.584  96.803  1.00 65.74      A    N
ATOM   3053  CA  GLY A 395      61.468 125.320  95.453  1.00 63.57      A    C
ATOM   3054  C   GLY A 395      60.352 126.274  95.062  1.00 62.10      A    C
ATOM   3055  O   GLY A 395      59.292 125.859  94.581  1.00 61.45      A    O
ATOM   3056  N   ILE A 396      60.606 127.562  95.266  1.00 60.92      A    N
ATOM   3057  CA  ILE A 396      59.642 128.611  94.969  1.00 60.40      A    C
ATOM   3058  CB  ILE A 396      59.050 129.157  96.301  1.00 61.57      A    C
ATOM   3059  CG2 ILE A 396      58.705 130.639  96.195  1.00 61.75      A    C
ATOM   3060  CG1 ILE A 396      57.839 128.301  96.691  1.00 62.07      A    C
ATOM   3061  CD1 ILE A 396      57.099 128.780  97.920  1.00 63.72      A    C
ATOM   3062  C   ILE A 396      60.267 129.738  94.149  1.00 58.89      A    C
ATOM   3063  O   ILE A 396      61.485 129.885  94.117  1.00 58.38      A    O
ATOM   3064  N   VAL A 397      59.426 130.524  93.481  1.00 58.58      A    N
ATOM   3065  CA  VAL A 397      59.887 131.645  92.660  1.00 57.41      A    C
ATOM   3066  CB  VAL A 397      59.943 131.246  91.153  1.00 56.14      A    C
ATOM   3067  CG1 VAL A 397      58.591 130.725  90.708  1.00 52.57      A    C
ATOM   3068  CG2 VAL A 397      60.352 132.448  90.301  1.00 54.94      A    C
ATOM   3069  C   VAL A 397      58.961 132.854  92.815  1.00 56.98      A    C
ATOM   3070  O   VAL A 397      57.743 132.708  92.765  1.00 55.73      A    O
ATOM   3071  N   ASN A 398      59.537 134.042  93.001  1.00 57.25      A    N
ATOM   3072  CA  ASN A 398      58.731 135.256  93.147  1.00 58.53      A    C
ATOM   3073  CB  ASN A 398      59.453 136.283  94.025  1.00 60.16      A    C
ATOM   3074  CG  ASN A 398      59.646 135.800  95.461  1.00 63.30      A    C
ATOM   3075  OD1 ASN A 398      58.731 135.224  96.064  1.00 64.34      A    O
ATOM   3076  ND2 ASN A 398      60.832 136.050  96.022  1.00 60.54      A    N
ATOM   3077  C   ASN A 398      58.410 135.882  91.787  1.00 59.54      A    C
ATOM   3078  O   ASN A 398      59.312 136.275  91.041  1.00 60.00      A    O
ATOM   3079  N   VAL A 399      57.123 135.974  91.464  1.00 59.53      A    N
ATOM   3080  CA  VAL A 399      56.702 136.545  90.189  1.00 59.41      A    C
ATOM   3081  CB  VAL A 399      55.686 135.632  89.465  1.00 57.18      A    C
ATOM   3082  CG1 VAL A 399      55.427 136.154  88.064  1.00 55.71      A    C
ATOM   3083  CG2 VAL A 399      56.206 134.211  89.409  1.00 56.52      A    C
ATOM   3084  C   VAL A 399      56.068 137.915  90.394  1.00 60.49      A    C
ATOM   3085  O   VAL A 399      54.976 138.024  90.937  1.00 60.85      A    O
ATOM   3086  N   LYS A 400      56.761 138.956  89.942  1.00 62.64      A    N
ATOM   3087  CA  LYS A 400      56.285 140.327  90.084  1.00 64.52      A    C
ATOM   3088  CB  LYS A 400      57.414 141.205  90.633  1.00 63.85      A    C
ATOM   3089  CG  LYS A 400      57.031 142.652  90.914  1.00 64.30      A    C
ATOM   3090  CD  LYS A 400      58.238 143.435  91.423  1.00 63.79      A    C
ATOM   3091  CE  LYS A 400      57.955 144.923  91.512  1.00 63.61      A    C
ATOM   3092  NZ  LYS A 400      59.179 145.682  91.908  1.00 65.99      A    N
ATOM   3093  C   LYS A 400      55.778 140.896  88.759  1.00 66.20      A    C
ATOM   3094  O   LYS A 400      56.404 140.711  87.708  1.00 64.79      A    O
ATOM   3095  N   SER A 401      54.634 141.576  88.819  1.00 67.79      A    N
ATOM   3096  CA  SER A 401      54.029 142.190  87.639  1.00 70.72      A    C
ATOM   3097  CB  SER A 401      52.502 142.135  87.732  1.00 71.89      A    C
ATOM   3098  OG  SER A 401      51.901 142.842  86.657  1.00 72.69      A    O
ATOM   3099  C   SER A 401      54.478 143.641  87.551  1.00 71.41      A    C
ATOM   3100  O   SER A 401      54.005 144.483  88.309  1.00 71.62      A    O
ATOM   3101  N   MET A 402      55.387 143.931  86.625  1.00 72.51      A    N
ATOM   3102  CA  MET A 402      55.903 145.285  86.469  1.00 74.30      A    C
ATOM   3103  CB  MET A 402      56.924 145.339  85.328  1.00 74.65      A    C
ATOM   3104  CG  MET A 402      58.096 144.390  85.532  1.00 75.26      A    C
ATOM   3105  SD  MET A 402      58.576 144.268  87.274  1.00 75.52      A    S
ATOM   3106  CE  MET A 402      59.337 145.881  87.540  1.00 76.51      A    C
ATOM   3107  C   MET A 402      54.802 146.306  86.233  1.00 74.77      A    C
ATOM   3108  O   MET A 402      55.020 147.507  86.384  1.00 74.57      A    O
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FIGURE 11-61

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ATOM   3109  N   ALA A 403      53.620 145.826  85.861  1.00 75.46      A    N
ATOM   3110  CA  ALA A 403      52.488 146.710  85.633  1.00 76.29      A    C
ATOM   3111  CB  ALA A 403      51.387 145.969  84.879  1.00 76.40      A    C
ATOM   3112  C   ALA A 403      51.966 147.218  86.980  1.00 76.87      A    C
ATOM   3113  O   ALA A 403      51.986 148.415  87.246  1.00 77.27      A    O
ATOM   3114  N   THR A 404      51.517 146.303  87.835  1.00 78.12      A    N
ATOM   3115  CA  THR A 404      50.987 146.674  89.148  1.00 79.78      A    C
ATOM   3116  CB  THR A 404      49.973 145.632  89.658  1.00 79.75      A    C
ATOM   3117  OG1 THR A 404      50.671 144.442  90.052  1.00 81.04      A    O
ATOM   3118  CG2 THR A 404      48.965 145.289  88.564  1.00 79.17      A    C
ATOM   3119  C   THR A 404      52.079 146.809  90.208  1.00 80.96      A    C
ATOM   3120  O   THR A 404      51.862 147.410  91.261  1.00 81.19      A    O
ATOM   3121  N   ARG A 405      53.246 146.238  89.925  1.00 82.13      A    N
ATOM   3122  CA  ARG A 405      54.387 146.269  90.838  1.00 83.06      A    C
ATOM   3123  CB  ARG A 405      54.621 147.685  91.371  1.00 84.67      A    C
ATOM   3124  CG  ARG A 405      54.747 148.733  90.283  1.00 88.01      A    C
ATOM   3125  CD  ARG A 405      54.845 150.128  90.875  1.00 91.23      A    C
ATOM   3126  NE  ARG A 405      54.525 151.159  89.891  1.00 93.00      A    N
ATOM   3127  CZ  ARG A 405      54.479 152.462  90.157  1.00 94.27      A    C
ATOM   3128  NH1 ARG A 405      54.738 152.904  91.383  1.00 94.56      A    N
ATOM   3129  NH2 ARG A 405      54.162 153.324  89.198  1.00 94.96      A    N
ATOM   3130  C   ARG A 405      54.150 145.312  91.996  1.00 82.54      A    C
ATOM   3131  O   ARG A 405      54.753 145.440  93.064  1.00 82.65      A    O
ATOM   3132  N   GLU A 406      53.266 144.347  91.772  1.00 82.23      A    N
ATOM   3133  CA  GLU A 406      52.947 143.356  92.788  1.00 81.76      A    C
ATOM   3134  CB  GLU A 406      51.436 143.283  92.994  1.00 82.58      A    C
ATOM   3135  CG  GLU A 406      51.000 142.133  93.882  1.00 84.03      A    C
ATOM   3136  CD  GLU A 406      49.558 142.254  94.326  1.00 85.02      A    C
ATOM   3137  OE1 GLU A 406      49.024 141.279  94.897  1.00 85.57      A    O
ATOM   3138  OE2 GLU A 406      48.961 143.329  94.111  1.00 85.41      A    O
ATOM   3139  C   GLU A 406      53.476 141.979  92.409  1.00 80.88      A    C
ATOM   3140  O   GLU A 406      53.392 141.567  91.253  1.00 80.82      A    O
ATOM   3141  N   GLU A 407      54.028 141.272  93.389  1.00 79.97      A    N
ATOM   3142  CA  GLU A 407      54.555 139.938  93.152  1.00 78.81      A    C
ATOM   3143  CB  GLU A 407      56.081 139.932  93.262  1.00 78.70      A    C
ATOM   3144  CG  GLU A 407      56.639 140.519  94.538  1.00 79.23      A    C
ATOM   3145  CD  GLU A 407      58.159 140.541  94.533  1.00 79.64      A    C
ATOM   3146  OE1 GLU A 407      58.774 139.452  94.480  1.00 78.21      A    O
ATOM   3147  OE2 GLU A 407      58.737 141.650  94.575  1.00 79.62      A    O
ATOM   3148  C   GLU A 407      53.967 138.915  94.109  1.00 77.72      A    C
ATOM   3149  O   GLU A 407      53.650 139.226  95.259  1.00 77.74      A    O
ATOM   3150  N   LYS A 408      53.817 137.693  93.612  1.00 76.42      A    N
ATOM   3151  CA  LYS A 408      53.269 136.593  94.393  1.00 75.36      A    C
ATOM   3152  CB  LYS A 408      51.906 136.184  93.824  1.00 76.46      A    C
ATOM   3153  CG  LYS A 408      51.269 134.966  94.475  1.00 77.08      A    C
ATOM   3154  CD  LYS A 408      49.894 134.685  93.872  1.00 77.88      A    C
ATOM   3155  CE  LYS A 408      49.414 133.277  94.205  1.00 78.12      A    C
ATOM   3156  NZ  LYS A 408      49.448 133.002  95.671  1.00 78.57      A    N
ATOM   3157  C   LYS A 408      54.243 135.425  94.328  1.00 73.99      A    C
ATOM   3158  O   LYS A 408      54.808 135.143  93.271  1.00 74.17      A    O
ATOM   3159  N   ALA A 409      54.453 134.759  95.458  1.00 71.80      A    N
ATOM   3160  CA  ALA A 409      55.369 133.626  95.500  1.00 70.07      A    C
ATOM   3161  CB  ALA A 409      55.767 133.316  96.944  1.00 69.16      A    C
ATOM   3162  C   ALA A 409      54.707 132.411  94.859  1.00 68.49      A    C
ATOM   3163  O   ALA A 409      53.517 132.159  95.061  1.00 67.71      A    O
ATOM   3164  N   PHE A 410      55.485 131.669  94.077  1.00 66.72      A    N
ATOM   3165  CA  PHE A 410      54.979 130.482  93.402  1.00 65.19      A    C
ATOM   3166  CB  PHE A 410      54.741 130.741  91.915  1.00 64.52      A    C
ATOM   3167  CG  PHE A 410      53.511 131.535  91.614  1.00 64.74      A    C
ATOM   3168  CD1 PHE A 410      53.501 132.913  91.772  1.00 64.18      A    C
ATOM   3169  CD2 PHE A 410      52.376 130.904  91.119  1.00 65.14      A    C
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FIGURE 11-62

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ATOM   3170  CE1 PHE A 410      52.381 133.658  91.435  1.00 64.97      A    C
ATOM   3171  CE2 PHE A 410      51.250 131.636  90.778  1.00 66.74      A    C
ATOM   3172  CZ  PHE A 410      51.253 133.021  90.936  1.00 67.31      A    C
ATOM   3173  C   PHE A 410      55.934 129.311  93.487  1.00 64.56      A    C
ATOM   3174  O   PHE A 410      57.133 129.471  93.725  1.00 64.13      A    O
ATOM   3175  N   PRO A 411      55.401 128.100  93.304  1.00 63.88      A    N
ATOM   3176  CD  PRO A 411      53.971 127.738  93.328  1.00 63.51      A    C
ATOM   3177  CA  PRO A 411      56.246 126.911  93.349  1.00 62.60      A    C
ATOM   3178  CB  PRO A 411      55.256 125.808  93.699  1.00 62.99      A    C
ATOM   3179  CG  PRO A 411      54.008 126.262  93.003  1.00 63.95      A    C
ATOM   3180  C   PRO A 411      56.831 126.755  91.946  1.00 60.94      A    C
ATOM   3181  O   PRO A 411      56.125 126.934  90.954  1.00 59.44      A    O
ATOM   3182  N   LEU A 412      58.119 126.450  91.860  1.00 60.39      A    N
ATOM   3183  CA  LEU A 412      58.752 126.282  90.560  1.00 59.03      A    C
ATOM   3184  CB  LEU A 412      60.107 125.603  90.732  1.00 57.99      A    C
ATOM   3185  CG  LEU A 412      61.099 126.434  91.550  1.00 58.46      A    C
ATOM   3186  CD1 LEU A 412      62.410 125.670  91.696  1.00 56.90      A    C
ATOM   3187  CD2 LEU A 412      61.329 127.777  90.864  1.00 57.42      A    C
ATOM   3188  C   LEU A 412      57.874 125.472  89.607  1.00 59.13      A    C
ATOM   3189  O   LEU A 412      57.664 125.866  88.456  1.00 58.76      A    O
ATOM   3190  N   SER A 413      57.346 124.354  90.100  1.00 58.38      A    N
ATOM   3191  CA  SER A 413      56.498 123.477  89.298  1.00 57.80      A    C
ATOM   3192  CB  SER A 413      55.868 122.396  90.184  1.00 58.07      A    C
ATOM   3193  OG  SER A 413      54.976 122.970  91.125  1.00 60.02      A    O
ATOM   3194  C   SER A 413      55.395 124.244  88.574  1.00 56.55      A    C
ATOM   3195  O   SER A 413      54.987 123.877  87.472  1.00 55.71      A    O
ATOM   3196  N   ALA A 414      54.908 125.307  89.201  1.00 55.51      A    N
ATOM   3197  CA  ALA A 414      53.855 126.115  88.603  1.00 56.43      A    C
ATOM   3198  CB  ALA A 414      53.449 127.234  89.561  1.00 55.40      A    C
ATOM   3199  C   ALA A 414      54.338 126.700  87.271  1.00 57.38      A    C
ATOM   3200  O   ALA A 414      53.599 126.706  86.278  1.00 55.58      A    O
ATOM   3201  N   ILE A 415      55.583 127.180  87.260  1.00 57.61      A    N
ATOM   3202  CA  ILE A 415      56.174 127.772  86.064  1.00 58.71      A    C
ATOM   3203  CB  ILE A 415      57.521 128.479  86.380  1.00 59.61      A    C
ATOM   3204  CG2 ILE A 415      58.101 129.088  85.105  1.00 56.11      A    C
ATOM   3205  CG1 ILE A 415      57.322 129.549  87.459  1.00 57.45      A    C
ATOM   3206  CD1 ILE A 415      56.355 130.637  87.079  1.00 58.37      A    C
ATOM   3207  C   ILE A 415      56.438 126.730  84.985  1.00 59.74      A    C
ATOM   3208  O   ILE A 415      56.122 126.942  83.814  1.00 59.56      A    O
ATOM   3209  N   HIS A 416      57.022 125.605  85.376  1.00 60.67      A    N
ATOM   3210  CA  HIS A 416      57.330 124.564  84.410  1.00 62.87      A    C
ATOM   3211  CB  HIS A 416      58.292 123.550  85.027  1.00 63.43      A    C
ATOM   3212  CG  HIS A 416      59.544 124.161  85.579  1.00 66.10      A    C
ATOM   3213  CD2 HIS A 416      60.831 124.091  85.161  1.00 66.41      A    C
ATOM   3214  ND1 HIS A 416      59.550 124.959  86.702  1.00 66.86      A    N
ATOM   3215  CE1 HIS A 416      60.786 125.352  86.953  1.00 66.36      A    C
ATOM   3216  NE2 HIS A 416      61.582 124.839  86.033  1.00 65.39      A    N
ATOM   3217  C   HIS A 416      56.088 123.845  83.885  1.00 63.87      A    C
ATOM   3218  O   HIS A 416      55.945 123.638  82.680  1.00 63.14      A    O
ATOM   3219  N   ASP A 417      55.183 123.481  84.788  1.00 65.44      A    N
ATOM   3220  CA  ASP A 417      53.981 122.756  84.394  1.00 67.04      A    C
ATOM   3221  CB  ASP A 417      53.507 121.840  85.530  1.00 67.61      A    C
ATOM   3222  CG  ASP A 417      54.552 120.814  85.929  1.00 68.75      A    C
ATOM   3223  OD1 ASP A 417      55.316 120.365  85.042  1.00 69.75      A    O
ATOM   3224  OD2 ASP A 417      54.602 120.447  87.126  1.00 68.98      A    O
ATOM   3225  C   ASP A 417      52.822 123.626  83.937  1.00 67.35      A    C
ATOM   3226  O   ASP A 417      51.855 123.119  83.366  1.00 67.14      A    O
ATOM   3227  N   SER A 418      52.901 124.930  84.174  1.00 68.19      A    N
ATOM   3228  CA  SER A 418      51.809 125.797  83.751  1.00 68.64      A    C
ATOM   3229  CB  SER A 418      50.529 125.408  84.504  1.00 69.77      A    C
ATOM   3230  OG  SER A 418      50.775 125.255  85.894  1.00 70.29      A    O
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FIGURE 11-63

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ATOM   3231  C   SER A 418      52.058 127.294  83.887  1.00 68.16      A    C
ATOM   3232  O   SER A 418      51.391 127.975  84.666  1.00 68.26      A    O
ATOM   3233  N   PHE A 419      53.017 127.806  83.124  1.00 68.06      A    N
ATOM   3234  CA  PHE A 419      53.312 129.233  83.151  1.00 68.32      A    C
ATOM   3235  CB  PHE A 419      54.548 129.537  82.304  1.00 65.44      A    C
ATOM   3236  CG  PHE A 419      54.968 130.975  82.348  1.00 63.12      A    C
ATOM   3237  CD1 PHE A 419      55.331 131.569  83.555  1.00 62.31      A    C
ATOM   3238  CD2 PHE A 419      54.989 131.741  81.192  1.00 58.49      A    C
ATOM   3239  CE1 PHE A 419      55.708 132.905  83.604  1.00 61.66      A    C
ATOM   3240  CE2 PHE A 419      55.362 133.070  81.232  1.00 59.17      A    C
ATOM   3241  CZ  PHE A 419      55.723 133.658  82.439  1.00 59.43      A    C
ATOM   3242  C   PHE A 419      52.082 129.921  82.562  1.00 70.06      A    C
ATOM   3243  O   PHE A 419      51.742 131.057  82.908  1.00 69.08      A    O
ATOM   3244  N   ASP A 420      51.426 129.192  81.665  1.00 73.01      A    N
ATOM   3245  CA  ASP A 420      50.206 129.622  80.996  1.00 75.09      A    C
ATOM   3246  CB  ASP A 420      49.525 128.389  80.391  1.00 76.65      A    C
ATOM   3247  CG  ASP A 420      48.356 128.736  79.492  1.00 79.28      A    C
ATOM   3248  OD1 ASP A 420      47.437 129.452  79.944  1.00 80.68      A    O
ATOM   3249  OD2 ASP A 420      48.352 128.278  78.328  1.00 80.61      A    O
ATOM   3250  C   ASP A 420      49.290 130.258  82.041  1.00 76.01      A    C
ATOM   3251  O   ASP A 420      48.761 131.355  81.843  1.00 75.80      A    O
ATOM   3252  N   GLU A 421      49.135 129.556  83.162  1.00 76.56      A    N
ATOM   3253  CA  GLU A 421      48.280 129.981  84.271  1.00 77.80      A    C
ATOM   3254  CB  GLU A 421      48.055 128.803  85.230  1.00 78.98      A    C
ATOM   3255  CG  GLU A 421      47.894 127.441  84.549  1.00 80.33      A    C
ATOM   3256  CD  GLU A 421      46.450 127.061  84.297  1.00 80.22      A    C
ATOM   3257  OE1 GLU A 421      45.694 126.927  85.284  1.00 80.96      A    O
ATOM   3258  OE2 GLU A 421      46.076 126.890  83.115  1.00 80.37      A    O
ATOM   3259  C   GLU A 421      48.849 131.157  85.067  1.00 77.92      A    C
ATOM   3260  O   GLU A 421      48.144 132.132  85.334  1.00 77.85      A    O
ATOM   3261  N   VAL A 422      50.118 131.052  85.460  1.00 77.84      A    N
ATOM   3262  CA  VAL A 422      50.771 132.102  86.242  1.00 77.40      A    C
ATOM   3263  CB  VAL A 422      52.253 131.749  86.545  1.00 77.03      A    C
ATOM   3264  CG1 VAL A 422      52.883 132.833  87.402  1.00 75.87      A    C
ATOM   3265  CG2 VAL A 422      52.336 130.407  87.259  1.00 76.01      A    C
ATOM   3266  C   VAL A 422      50.723 133.446  85.522  1.00 77.78      A    C
ATOM   3267  O   VAL A 422      50.536 134.490  86.148  1.00 76.95      A    O
ATOM   3268  N   TYR A 423      50.891 133.419  84.206  1.00 78.27      A    N
ATOM   3269  CA  TYR A 423      50.854 134.649  83.430  1.00 79.64      A    C
ATOM   3270  CB  TYR A 423      51.034 134.342  81.941  1.00 80.33      A    C
ATOM   3271  CG  TYR A 423      51.166 135.569  81.063  1.00 80.88      A    C
ATOM   3272  CD1 TYR A 423      52.355 136.294  81.017  1.00 81.22      A    C
ATOM   3273  CE1 TYR A 423      52.486 137.416  80.196  1.00 81.69      A    C
ATOM   3274  CD2 TYR A 423      50.103 135.999  80.269  1.00 81.34      A    C
ATOM   3275  CE2 TYR A 423      50.223 137.119  79.446  1.00 81.83      A    C
ATOM   3276  CZ  TYR A 423      51.417 137.820  79.414  1.00 82.04      A    C
ATOM   3277  OH  TYR A 423      51.540 138.920  78.595  1.00 82.85      A    O
ATOM   3278  C   TYR A 423      49.513 135.344  83.655  1.00 79.96      A    C
ATOM   3279  O   TYR A 423      49.454 136.420  84.256  1.00 79.85      A    O
ATOM   3280  N   ASP A 424      48.440 134.713  83.185  1.00 80.28      A    N
ATOM   3281  CA  ASP A 424      47.095 135.264  83.317  1.00 80.96      A    C
ATOM   3282  CB  ASP A 424      46.060 134.216  82.916  1.00 82.15      A    C
ATOM   3283  CG  ASP A 424      46.207 133.783  81.476  1.00 83.83      A    C
ATOM   3284  OD1 ASP A 424      46.285 134.668  80.596  1.00 83.75      A    O
ATOM   3285  OD2 ASP A 424      46.242 132.561  81.223  1.00 85.42      A    O
ATOM   3286  C   ASP A 424      46.779 135.788  84.712  1.00 80.51      A    C
ATOM   3287  O   ASP A 424      46.324 136.921  84.866  1.00 80.08      A    O
ATOM   3288  N   GLU A 425      47.015 134.961  85.724  1.00 80.77      A    N
ATOM   3289  CA  GLU A 425      46.755 135.357  87.103  1.00 81.36      A    C
ATOM   3290  CB  GLU A 425      47.158 134.228  88.058  1.00 80.76      A    C
ATOM   3291  CG  GLU A 425      47.212 134.627  89.533  1.00 81.08      A    C
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FIGURE 11-64

ATOM	3292	CD	GLU	A	425	47.502	133.448	90.457	1.00	81.15	A	C
ATOM	3293	OE1	GLU	A	425	47.907	133.690	91.618	1.00	79.35	A	O
ATOM	3294	OE2	GLU	A	425	47.316	132.284	90.027	1.00	81.14	A	O
ATOM	3295	C	GLU	A	425	47.500	136.639	87.459	1.00	82.82	A	C
ATOM	3296	O	GLU	A	425	46.920	137.556	88.040	1.00	82.59	A	O
ATOM	3297	N	MET	A	426	48.780	136.707	87.096	1.00	84.89	A	N
ATOM	3298	CA	MET	A	426	49.602	137.879	87.393	1.00	86.13	A	C
ATOM	3299	CB	MET	A	426	51.085	137.518	87.325	1.00	84.82	A	C
ATOM	3300	CG	MET	A	426	51.536	136.584	88.434	1.00	83.33	A	C
ATOM	3301	SD	MET	A	426	51.031	137.151	90.077	1.00	82.46	A	S
ATOM	3302	CE	MET	A	426	52.174	138.494	90.369	1.00	81.48	A	C
ATOM	3303	C	MET	A	426	49.333	139.094	86.510	1.00	88.28	A	C
ATOM	3304	O	MET	A	426	49.510	140.232	86.953	1.00	89.17	A	O
ATOM	3305	N	MET	A	427	48.921	138.866	85.265	1.00	89.80	A	N
ATOM	3306	CA	MET	A	427	48.619	139.978	84.366	1.00	91.81	A	C
ATOM	3307	CB	MET	A	427	48.497	139.489	82.920	1.00	91.94	A	C
ATOM	3308	CG	MET	A	427	49.831	139.147	82.268	1.00	92.17	A	C
ATOM	3309	SD	MET	A	427	50.929	140.580	82.116	1.00	91.75	A	S
ATOM	3310	CE	MET	A	427	51.774	140.530	83.679	1.00	91.49	A	C
ATOM	3311	C	MET	A	427	47.317	140.639	84.810	1.00	92.89	A	C
ATOM	3312	O	MET	A	427	47.279	141.314	85.841	1.00	93.85	A	O
ATOM	3313	N	THR	A	428	46.254	140.448	84.036	1.00	93.67	A	N
ATOM	3314	CA	THR	A	428	44.958	141.019	84.383	1.00	94.14	A	C
ATOM	3315	CB	THR	A	428	43.941	140.863	83.221	1.00	94.34	A	C
ATOM	3316	OG1	THR	A	428	44.196	139.641	82.516	1.00	94.34	A	O
ATOM	3317	CG2	THR	A	428	44.037	142.047	82.260	1.00	93.90	A	C
ATOM	3318	C	THR	A	428	44.409	140.352	85.650	1.00	94.43	A	C
ATOM	3319	O	THR	A	428	43.626	139.383	85.533	1.00	94.69	A	O
ATOM	3320	OXT	THR	A	428	44.793	140.795	86.755	1.00	94.15	A	O
TER	3321		THR	A	428						A	
ATOM	3322	CB	ALA	A	999	69.262	156.347	40.713	1.00	69.50	A	C
ATOM	3323	C	ALA	A	999	67.800	156.250	38.664	1.00	71.70	A	C
ATOM	3324	O	ALA	A	999	67.696	157.000	37.686	1.00	73.37	A	O
ATOM	3325	N	ALA	A	999	66.802	156.458	40.943	1.00	70.69	A	N
ATOM	3326	CA	ALA	A	999	67.956	156.831	40.077	1.00	71.32	A	C
ATOM	3327	N	HIS	A	1000	67.786	154.922	38.556	1.00	70.84	A	N
ATOM	3328	CA	HIS	A	1000	67.643	154.250	37.261	1.00	69.70	A	C
ATOM	3329	CB	HIS	A	1000	68.940	154.374	36.440	1.00	73.75	A	C
ATOM	3330	CG	HIS	A	1000	70.162	154.637	37.268	1.00	77.03	A	C
ATOM	3331	CD2	HIS	A	1000	71.005	155.698	37.297	1.00	77.74	A	C
ATOM	3332	ND1	HIS	A	1000	70.613	153.762	38.234	1.00	78.83	A	N
ATOM	3333	CE1	HIS	A	1000	71.680	154.274	38.824	1.00	79.59	A	C
ATOM	3334	NE2	HIS	A	1000	71.938	155.448	38.275	1.00	79.27	A	N
ATOM	3335	C	HIS	A	1000	67.274	152.779	37.416	1.00	66.69	A	C
ATOM	3336	O	HIS	A	1000	68.038	151.996	37.978	1.00	67.01	A	O
ATOM	3337	N	HIS	A	1001	66.105	152.417	36.894	1.00	63.01	A	N
ATOM	3338	CA	HIS	A	1001	65.574	151.056	36.959	1.00	59.50	A	C
ATOM	3339	CB	HIS	A	1001	64.213	151.017	36.264	1.00	55.64	A	C
ATOM	3340	CG	HIS	A	1001	63.551	149.672	36.266	1.00	49.55	A	C
ATOM	3341	CD2	HIS	A	1001	63.833	148.534	36.944	1.00	49.16	A	C
ATOM	3342	ND1	HIS	A	1001	62.483	149.374	35.445	1.00	46.95	A	N
ATOM	3343	CE1	HIS	A	1001	62.141	148.109	35.609	1.00	45.23	A	C
ATOM	3344	NE2	HIS	A	1001	62.945	147.576	36.513	1.00	47.59	A	N
ATOM	3345	C	HIS	A	1001	66.484	149.981	36.364	1.00	59.45	A	C
ATOM	3346	O	HIS	A	1001	67.052	149.161	37.081	1.00	60.04	A	O
ATOM	3347	N	HIS	A	1002	66.616	149.969	35.052	1.00	59.28	A	N
ATOM	3348	CA	HIS	A	1002	67.450	148.963	34.412	1.00	60.05	A	C
ATOM	3349	CB	HIS	A	1002	66.680	148.406	33.205	1.00	60.19	A	C
ATOM	3350	CG	HIS	A	1002	67.451	147.443	32.354	1.00	58.74	A	C
ATOM	3351	CD2	HIS	A	1002	67.664	147.417	31.017	1.00	56.41	A	C
ATOM	3352	ND1	HIS	A	1002	68.057	146.312	32.861	1.00	57.18	A	N

FIGURE 11-65

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ATOM   3353  CE1 HIS A1002      68.607 145.632  31.872  1.00 55.88      A    C
ATOM   3354  NE2 HIS A1002      68.383 146.281  30.743  1.00 55.24      A    N
ATOM   3355  C   HIS A1002      68.809 149.553  34.012  1.00 61.11      A    C
ATOM   3356  O   HIS A1002      69.044 150.757  34.151  1.00 59.85      A    O
ATOM   3357  N   ALA A1003      69.700 148.685  33.541  1.00 63.46      A    N
ATOM   3358  CA  ALA A1003      71.044 149.058  33.096  1.00 65.24      A    C
ATOM   3359  CB  ALA A1003      70.990 149.560  31.638  1.00 65.10      A    C
ATOM   3360  C   ALA A1003      71.727 150.096  33.993  1.00 65.89      A    C
ATOM   3361  O   ALA A1003      72.139 151.151  33.456  1.00 65.88      A    O
ATOM   3362  OXT ALA A1003      71.857 149.832  35.214  1.00 64.31      A    O
TER    3363      ALA A1003                                              A
ATOM   3364  CB  LYS B   5     73.188 130.978  33.215  1.00 83.75      B    C
ATOM   3365  CG  LYS B   5     72.456 130.607  31.929  1.00 83.31      B    C
ATOM   3366  CD  LYS B   5     72.457 131.746  30.928  1.00 82.36      B    C
ATOM   3367  CE  LYS B   5     71.502 131.460  29.784  1.00 81.42      B    C
ATOM   3368  NZ  LYS B   5     71.400 132.618  28.855  1.00 81.99      B    N
ATOM   3369  C   LYS B   5     74.409 129.557  34.863  1.00 85.59      B    C
ATOM   3370  O   LYS B   5     74.958 128.513  34.493  1.00 86.09      B    O
ATOM   3371  N   LYS B   5     72.121 130.444  35.399  1.00 84.31      B    N
ATOM   3372  CA  LYS B   5     73.032 129.937  34.332  1.00 84.86      B    C
ATOM   3373  N   PRO B   6     74.989 130.396  35.739  1.00 85.91      B    N
ATOM   3374  CD  PRO B   6     74.506 131.707  36.210  1.00 86.09      B    C
ATOM   3375  CA  PRO B   6     76.314 130.102  36.296  1.00 85.70      B    C
ATOM   3376  CB  PRO B   6     76.516 131.224  37.312  1.00 85.64      B    C
ATOM   3377  CG  PRO B   6     75.783 132.367  36.679  1.00 85.79      B    C
ATOM   3378  C   PRO B   6     76.426 128.716  36.929  1.00 85.00      B    C
ATOM   3379  O   PRO B   6     75.586 128.308  37.733  1.00 84.23      B    O
ATOM   3380  N   LYS B   7     77.470 127.991  36.548  1.00 84.65      B    N
ATOM   3381  CA  LYS B   7     77.702 126.660  37.084  1.00 83.87      B    C
ATOM   3382  CB  LYS B   7     78.947 126.060  36.436  1.00 84.81      B    C
ATOM   3383  CG  LYS B   7     78.752 125.556  35.008  1.00 84.86      B    C
ATOM   3384  CD  LYS B   7     78.157 124.156  35.004  1.00 84.59      B    C
ATOM   3385  CE  LYS B   7     78.290 123.500  33.640  1.00 84.23      B    C
ATOM   3386  NZ  LYS B   7     77.908 122.063  33.698  1.00 83.92      B    N
ATOM   3387  C   LYS B   7     77.895 126.759  38.594  1.00 82.95      B    C
ATOM   3388  O   LYS B   7     78.518 127.700  39.085  1.00 83.04      B    O
ATOM   3389  N   GLY B   8     77.351 125.793  39.326  1.00 82.03      B    N
ATOM   3390  CA  GLY B   8     77.488 125.801  40.772  1.00 81.26      B    C
ATOM   3391  C   GLY B   8     76.521 126.745  41.464  1.00 80.93      B    C
ATOM   3392  O   GLY B   8     76.655 127.024  42.662  1.00 81.36      B    O
ATOM   3393  N   THR B   9     75.549 127.251  40.711  1.00 78.83      B    N
ATOM   3394  CA  THR B   9     74.552 128.153  41.271  1.00 77.09      B    C
ATOM   3395  CB  THR B   9     74.794 129.630  40.849  1.00 79.21      B    C
ATOM   3396  OG1 THR B   9     74.622 129.763  39.432  1.00 80.77      B    O
ATOM   3397  CG2 THR B   9     76.205 130.082  41.236  1.00 79.47      B    C
ATOM   3398  C   THR B   9     73.166 127.734  40.805  1.00 73.93      B    C
ATOM   3399  O   THR B   9     73.022 126.988  39.837  1.00 73.45      B    O
ATOM   3400  N   ASN B  10     72.147 128.216  41.503  1.00 70.73      B    N
ATOM   3401  CA  ASN B  10     70.773 127.890  41.158  1.00 67.48      B    C
ATOM   3402  CB  ASN B  10     70.226 126.813  42.105  1.00 69.89      B    C
ATOM   3403  CG  ASN B  10     71.284 125.809  42.542  1.00 72.89      B    C
ATOM   3404  OD1 ASN B  10     71.676 124.917  41.781  1.00 72.79      B    O
ATOM   3405  ND2 ASN B  10     71.756 125.955  43.781  1.00 73.37      B    N
ATOM   3406  C   ASN B  10     69.914 129.135  41.319  1.00 62.95      B    C
ATOM   3407  O   ASN B  10     70.165 129.947  42.209  1.00 61.58      B    O
ATOM   3408  N   ASP B  11     68.919 129.301  40.452  1.00 58.15      B    N
ATOM   3409  CA  ASP B  11     68.002 130.419  40.604  1.00 52.83      B    C
ATOM   3410  CB  ASP B  11     67.287 130.770  39.303  1.00 53.10      B    C
ATOM   3411  CG  ASP B  11     68.231 131.117  38.184  1.00 53.83      B    C
ATOM   3412  OD1 ASP B  11     69.236 131.822  38.429  1.00 54.14      B    O
ATOM   3413  OD2 ASP B  11     67.950 130.691  37.045  1.00 54.59      B    O
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FIGURE 11-66

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ATOM   3414  C   ASP B  11      66.974 129.837  41.550  1.00 49.45      B    C
ATOM   3415  O   ASP B  11      66.700 128.652  41.492  1.00 49.66      B    O
ATOM   3416  N   ILE B  12      66.428 130.637  42.449  1.00 48.62      B    N
ATOM   3417  CA  ILE B  12      65.404 130.113  43.336  1.00 46.85      B    C
ATOM   3418  CB  ILE B  12      65.629 130.517  44.822  1.00 47.15      B    C
ATOM   3419  CG2 ILE B  12      64.386 130.161  45.649  1.00 44.03      B    C
ATOM   3420  CG1 ILE B  12      66.802 129.728  45.421  1.00 46.73      B    C
ATOM   3421  CD1 ILE B  12      68.063 129.747  44.619  1.00 48.15      B    C
ATOM   3422  C   ILE B  12      64.136 130.735  42.794  1.00 45.29      B    C
ATOM   3423  O   ILE B  12      63.907 131.931  42.947  1.00 44.70      B    O
ATOM   3424  N   LEU B  13      63.333 129.905  42.135  1.00 45.84      B    N
ATOM   3425  CA  LEU B  13      62.093 130.338  41.504  1.00 44.84      B    C
ATOM   3426  CB  LEU B  13      61.810 129.458  40.291  1.00 43.83      B    C
ATOM   3427  CG  LEU B  13      62.955 129.365  39.291  1.00 43.13      B    C
ATOM   3428  CD1 LEU B  13      62.576 128.415  38.165  1.00 43.07      B    C
ATOM   3429  CD2 LEU B  13      63.257 130.751  38.751  1.00 40.30      B    C
ATOM   3430  C   LEU B  13      60.859 130.344  42.381  1.00 45.40      B    C
ATOM   3431  O   LEU B  13      60.833 129.756  43.456  1.00 45.47      B    O
ATOM   3432  N   PRO B  14      59.816 131.046  41.930  1.00 48.34      B    N
ATOM   3433  CD  PRO B  14      59.780 132.005  40.809  1.00 49.35      B    C
ATOM   3434  CA  PRO B  14      58.577 131.099  42.699  1.00 49.81      B    C
ATOM   3435  CB  PRO B  14      57.643 131.877  41.779  1.00 49.97      B    C
ATOM   3436  CG  PRO B  14      58.582 132.873  41.162  1.00 50.65      B    C
ATOM   3437  C   PRO B  14      58.122 129.664  42.923  1.00 50.80      B    C
ATOM   3438  O   PRO B  14      58.520 128.747  42.194  1.00 52.34      B    O
ATOM   3439  N   GLY B  15      57.293 129.456  43.930  1.00 51.19      B    N
ATOM   3440  CA  GLY B  15      56.855 128.104  44.194  1.00 52.62      B    C
ATOM   3441  C   GLY B  15      57.832 127.444  45.140  1.00 53.01      B    C
ATOM   3442  O   GLY B  15      57.425 126.671  46.005  1.00 56.43      B    O
ATOM   3443  N   THR B  16      59.118 127.741  44.989  1.00 51.43      B    N
ATOM   3444  CA  THR B  16      60.118 127.163  45.875  1.00 49.67      B    C
ATOM   3445  CB  THR B  16      61.145 126.311  45.073  1.00 51.42      B    C
ATOM   3446  OG1 THR B  16      62.463 126.511  45.594  1.00 48.64      B    O
ATOM   3447  CG2 THR B  16      61.088 126.654  43.585  1.00 54.16      B    C
ATOM   3448  C   THR B  16      60.800 128.238  46.734  1.00 49.03      B    C
ATOM   3449  O   THR B  16      61.345 127.953  47.804  1.00 47.08      B    O
ATOM   3450  N   SER B  17      60.734 129.487  46.293  1.00 47.27      B    N
ATOM   3451  CA  SER B  17      61.329 130.561  47.071  1.00 46.03      B    C
ATOM   3452  CB  SER B  17      61.313 131.868  46.268  1.00 44.71      B    C
ATOM   3453  OG  SER B  17      59.996 132.277  45.953  1.00 43.47      B    O
ATOM   3454  C   SER B  17      60.583 130.726  48.408  1.00 47.22      B    C
ATOM   3455  O   SER B  17      61.160 131.171  49.402  1.00 45.93      B    O
ATOM   3456  N   GLU B  18      59.304 130.357  48.440  1.00 47.73      B    N
ATOM   3457  CA  GLU B  18      58.529 130.456  49.679  1.00 49.06      B    C
ATOM   3458  CB  GLU B  18      57.050 130.105  49.457  1.00 51.37      B    C
ATOM   3459  CG  GLU B  18      56.267 131.074  48.600  1.00 56.38      B    C
ATOM   3460  CD  GLU B  18      56.737 131.089  47.154  1.00 59.06      B    C
ATOM   3461  OE1 GLU B  18      57.245 130.042  46.689  1.00 58.30      B    O
ATOM   3462  OE2 GLU B  18      56.583 132.143  46.488  1.00 59.91      B    O
ATOM   3463  C   GLU B  18      59.087 129.516  50.745  1.00 47.12      B    C
ATOM   3464  O   GLU B  18      58.981 129.790  51.935  1.00 48.28      B    O
ATOM   3465  N   LYS B  19      59.662 128.396  50.330  1.00 46.17      B    N
ATOM   3466  CA  LYS B  19      60.224 127.470  51.307  1.00 46.57      B    C
ATOM   3467  CB  LYS B  19      60.749 126.200  50.623  1.00 47.69      B    C
ATOM   3468  CG  LYS B  19      59.660 125.403  49.901  1.00 51.03      B    C
ATOM   3469  CD  LYS B  19      60.170 124.073  49.347  1.00 53.25      B    C
ATOM   3470  CE  LYS B  19      59.042 123.306  48.653  1.00 55.43      B    C
ATOM   3471  NZ  LYS B  19      59.432 121.904  48.317  1.00 57.53      B    N
ATOM   3472  C   LYS B  19      61.354 128.205  52.013  1.00 45.93      B    C
ATOM   3473  O   LYS B  19      61.428 128.223  53.245  1.00 45.32      B    O
ATOM   3474  N   TRP B  20      62.224 128.823  51.221  1.00 44.51      B    N
```

FIGURE 11-67

ATOM	3475	CA	TRP	B	20	63.335	129.589	51.765	1.00	44.46	B	C
ATOM	3476	CB	TRP	B	20	64.133	130.251	50.638	1.00	44.67	B	C
ATOM	3477	CG	TRP	B	20	64.962	129.297	49.833	1.00	44.51	B	C
ATOM	3478	CD2	TRP	B	20	66.391	129.203	49.839	1.00	45.12	B	C
ATOM	3479	CE2	TRP	B	20	66.749	128.199	48.911	1.00	43.95	B	C
ATOM	3480	CE3	TRP	B	20	67.406	129.873	50.537	1.00	44.06	B	C
ATOM	3481	CD1	TRP	B	20	64.519	128.366	48.931	1.00	44.60	B	C
ATOM	3482	NE1	TRP	B	20	65.592	127.704	48.371	1.00	43.85	B	N
ATOM	3483	CZ2	TRP	B	20	68.079	127.852	48.666	1.00	45.31	B	C
ATOM	3484	CZ3	TRP	B	20	68.724	129.528	50.293	1.00	44.61	B	C
ATOM	3485	CH2	TRP	B	20	69.051	128.526	49.365	1.00	43.59	B	C
ATOM	3486	C	TRP	B	20	62.774	130.661	52.693	1.00	43.44	B	C
ATOM	3487	O	TRP	B	20	63.251	130.847	53.817	1.00	43.72	B	O
ATOM	3488	N	GLN	B	21	61.753	131.362	52.216	1.00	41.64	B	N
ATOM	3489	CA	GLN	B	21	61.126	132.408	53.008	1.00	41.12	B	C
ATOM	3490	CB	GLN	B	21	59.967	133.032	52.242	1.00	39.88	B	C
ATOM	3491	CG	GLN	B	21	60.383	134.085	51.256	1.00	40.69	B	C
ATOM	3492	CD	GLN	B	21	59.297	134.367	50.239	1.00	43.19	B	C
ATOM	3493	OE1	GLN	B	21	58.114	134.400	50.577	1.00	47.09	B	O
ATOM	3494	NE2	GLN	B	21	59.690	134.578	48.988	1.00	42.88	B	N
ATOM	3495	C	GLN	B	21	60.620	131.858	54.330	1.00	40.29	B	C
ATOM	3496	O	GLN	B	21	60.713	132.521	55.357	1.00	38.21	B	O
ATOM	3497	N	PHE	B	22	60.075	130.647	54.300	1.00	41.85	B	N
ATOM	3498	CA	PHE	B	22	59.563	130.036	55.517	1.00	41.83	B	C
ATOM	3499	CB	PHE	B	22	58.805	128.750	55.199	1.00	42.82	B	C
ATOM	3500	CG	PHE	B	22	58.362	127.997	56.420	1.00	43.84	B	C
ATOM	3501	CD1	PHE	B	22	57.413	128.539	57.280	1.00	44.48	B	C
ATOM	3502	CD2	PHE	B	22	58.904	126.751	56.718	1.00	43.12	B	C
ATOM	3503	CE1	PHE	B	22	57.007	127.844	58.428	1.00	45.79	B	C
ATOM	3504	CE2	PHE	B	22	58.509	126.052	57.854	1.00	44.62	B	C
ATOM	3505	CZ	PHE	B	22	57.558	126.598	58.713	1.00	45.62	B	C
ATOM	3506	C	PHE	B	22	60.703	129.727	56.484	1.00	41.79	B	C
ATOM	3507	O	PHE	B	22	60.641	130.059	57.666	1.00	42.80	B	O
ATOM	3508	N	VAL	B	23	61.747	129.087	55.986	1.00	40.95	B	N
ATOM	3509	CA	VAL	B	23	62.872	128.758	56.841	1.00	41.33	B	C
ATOM	3510	CB	VAL	B	23	63.981	128.088	56.039	1.00	42.12	B	C
ATOM	3511	CG1	VAL	B	23	65.182	127.819	56.937	1.00	41.26	B	C
ATOM	3512	CG2	VAL	B	23	63.451	126.796	55.434	1.00	44.08	B	C
ATOM	3513	C	VAL	B	23	63.430	130.016	57.487	1.00	40.11	B	C
ATOM	3514	O	VAL	B	23	63.620	130.084	58.701	1.00	38.32	B	O
ATOM	3515	N	GLU	B	24	63.684	131.009	56.646	1.00	40.96	B	N
ATOM	3516	CA	GLU	B	24	64.237	132.285	57.069	1.00	39.81	B	C
ATOM	3517	CB	GLU	B	24	64.433	133.180	55.833	1.00	40.35	B	C
ATOM	3518	CG	GLU	B	24	65.651	132.777	54.986	1.00	38.65	B	C
ATOM	3519	CD	GLU	B	24	65.585	133.222	53.524	1.00	38.76	B	C
ATOM	3520	OE1	GLU	B	24	64.732	134.065	53.167	1.00	35.38	B	O
ATOM	3521	OE2	GLU	B	24	66.417	132.723	52.727	1.00	40.18	B	O
ATOM	3522	C	GLU	B	24	63.370	132.980	58.111	1.00	40.97	B	C
ATOM	3523	O	GLU	B	24	63.875	133.515	59.094	1.00	38.20	B	O
ATOM	3524	N	GLU	B	25	62.059	132.955	57.898	1.00	42.60	B	N
ATOM	3525	CA	GLU	B	25	61.121	133.592	58.809	1.00	44.63	B	C
ATOM	3526	CB	GLU	B	25	59.731	133.625	58.162	1.00	48.67	B	C
ATOM	3527	CG	GLU	B	25	58.781	134.667	58.717	1.00	56.79	B	C
ATOM	3528	CD	GLU	B	25	57.614	134.949	57.767	1.00	64.52	B	C
ATOM	3529	OE1	GLU	B	25	57.868	135.385	56.610	1.00	65.43	B	O
ATOM	3530	OE2	GLU	B	25	56.446	134.735	58.178	1.00	66.26	B	O
ATOM	3531	C	GLU	B	25	61.078	132.845	60.145	1.00	42.34	B	C
ATOM	3532	O	GLU	B	25	60.913	133.443	61.204	1.00	40.87	B	O
ATOM	3533	N	THR	B	26	61.233	131.533	60.096	1.00	41.73	B	N
ATOM	3534	CA	THR	B	26	61.204	130.751	61.316	1.00	40.89	B	C
ATOM	3535	CB	THR	B	26	61.153	129.259	60.996	1.00	40.75	B	C

FIGURE 11-68

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ATOM   3536  OG1 THR B  26      59.950 128.993  60.264  1.00 40.41      B    O
ATOM   3537  CG2 THR B  26      61.169 128.422  62.282  1.00 36.39      B    C
ATOM   3538  C   THR B  26      62.426 131.081  62.170  1.00 41.65      B    C
ATOM   3539  O   THR B  26      62.307 131.289  63.381  1.00 42.81      B    O
ATOM   3540  N   ALA B  27      63.594 131.145  61.543  1.00 39.93      B    N
ATOM   3541  CA  ALA B  27      64.807 131.479  62.273  1.00 40.38      B    C
ATOM   3542  CB  ALA B  27      66.010 131.435  61.345  1.00 41.16      B    C
ATOM   3543  C   ALA B  27      64.666 132.872  62.888  1.00 41.12      B    C
ATOM   3544  O   ALA B  27      64.825 133.034  64.100  1.00 40.95      B    O
ATOM   3545  N   ARG B  28      64.342 133.871  62.065  1.00 41.32      B    N
ATOM   3546  CA  ARG B  28      64.190 135.240  62.558  1.00 41.96      B    C
ATOM   3547  CB  ARG B  28      63.667 136.169  61.460  1.00 45.52      B    C
ATOM   3548  CG  ARG B  28      64.662 136.479  60.376  1.00 47.44      B    C
ATOM   3549  CD  ARG B  28      64.207 137.672  59.548  1.00 52.20      B    C
ATOM   3550  NE  ARG B  28      64.278 137.399  58.111  1.00 54.70      B    N
ATOM   3551  CZ  ARG B  28      63.255 136.958  57.382  1.00 52.91      B    C
ATOM   3552  NH1 ARG B  28      62.075 136.744  57.946  1.00 53.20      B    N
ATOM   3553  NH2 ARG B  28      63.413 136.727  56.086  1.00 54.10      B    N
ATOM   3554  C   ARG B  28      63.280 135.381  63.775  1.00 42.15      B    C
ATOM   3555  O   ARG B  28      63.541 136.199  64.653  1.00 40.17      B    O
ATOM   3556  N   LEU B  29      62.207 134.599  63.818  1.00 43.81      B    N
ATOM   3557  CA  LEU B  29      61.271 134.660  64.933  1.00 46.45      B    C
ATOM   3558  CB  LEU B  29      59.963 133.952  64.567  1.00 48.47      B    C
ATOM   3559  CG  LEU B  29      59.108 134.649  63.500  1.00 51.20      B    C
ATOM   3560  CD1 LEU B  29      57.987 133.727  63.023  1.00 51.71      B    C
ATOM   3561  CD2 LEU B  29      58.529 135.919  64.084  1.00 52.77      B    C
ATOM   3562  C   LEU B  29      61.852 134.044  66.201  1.00 46.65      B    C
ATOM   3563  O   LEU B  29      61.787 134.641  67.272  1.00 47.61      B    O
ATOM   3564  N   ILE B  30      62.416 132.849  66.081  1.00 46.75      B    N
ATOM   3565  CA  ILE B  30      62.998 132.177  67.234  1.00 45.59      B    C
ATOM   3566  CB  ILE B  30      63.587 130.811  66.839  1.00 46.40      B    C
ATOM   3567  CG2 ILE B  30      63.915 130.020  68.078  1.00 48.00      B    C
ATOM   3568  CG1 ILE B  30      62.575 130.015  66.008  1.00 51.50      B    C
ATOM   3569  CD1 ILE B  30      61.311 129.595  66.760  1.00 52.35      B    C
ATOM   3570  C   ILE B  30      64.115 133.054  67.812  1.00 44.25      B    C
ATOM   3571  O   ILE B  30      64.123 133.373  69.004  1.00 43.02      B    O
ATOM   3572  N   PHE B  31      65.042 133.453  66.948  1.00 41.44      B    N
ATOM   3573  CA  PHE B  31      66.168 134.279  67.351  1.00 41.96      B    C
ATOM   3574  CB  PHE B  31      67.014 134.622  66.124  1.00 39.57      B    C
ATOM   3575  CG  PHE B  31      67.729 133.439  65.534  1.00 35.70      B    C
ATOM   3576  CD1 PHE B  31      68.142 133.448  64.209  1.00 35.38      B    C
ATOM   3577  CD2 PHE B  31      67.999 132.318  66.306  1.00 39.02      B    C
ATOM   3578  CE1 PHE B  31      68.813 132.357  63.658  1.00 32.01      B    C
ATOM   3579  CE2 PHE B  31      68.670 131.220  65.765  1.00 38.15      B    C
ATOM   3580  CZ  PHE B  31      69.075 131.249  64.430  1.00 36.29      B    C
ATOM   3581  C   PHE B  31      65.731 135.548  68.078  1.00 42.67      B    C
ATOM   3582  O   PHE B  31      66.320 135.925  69.093  1.00 41.37      B    O
ATOM   3583  N   LYS B  32      64.701 136.205  67.558  1.00 43.80      B    N
ATOM   3584  CA  LYS B  32      64.187 137.409  68.189  1.00 45.35      B    C
ATOM   3585  CB  LYS B  32      63.049 137.998  67.347  1.00 48.33      B    C
ATOM   3586  CG  LYS B  32      62.295 139.136  68.021  1.00 53.31      B    C
ATOM   3587  CD  LYS B  32      61.233 139.757  67.119  1.00 55.54      B    C
ATOM   3588  CE  LYS B  32      61.852 140.715  66.110  1.00 59.24      B    C
ATOM   3589  NZ  LYS B  32      60.814 141.493  65.362  1.00 62.54      B    N
ATOM   3590  C   LYS B  32      63.694 137.074  69.606  1.00 44.54      B    C
ATOM   3591  O   LYS B  32      63.903 137.854  70.541  1.00 41.86      B    O
ATOM   3592  N   ASP B  33      63.058 135.912  69.758  1.00 43.89      B    N
ATOM   3593  CA  ASP B  33      62.552 135.474  71.059  1.00 44.95      B    C
ATOM   3594  CB  ASP B  33      61.753 134.171  70.928  1.00 48.90      B    C
ATOM   3595  CG  ASP B  33      60.317 134.401  70.459  1.00 53.38      B    C
ATOM   3596  OD1 ASP B  33      59.634 135.280  71.033  1.00 54.51      B    O
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FIGURE 11-69

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ATOM   3597  OD2 ASP B  33      59.868 133.694  69.524  1.00 55.81      B    O
ATOM   3598  C   ASP B  33      63.675 135.260  72.072  1.00 44.75      B    C
ATOM   3599  O   ASP B  33      63.549 135.637  73.239  1.00 45.21      B    O
ATOM   3600  N   TYR B  34      64.767 134.647  71.626  1.00 41.25      B    N
ATOM   3601  CA  TYR B  34      65.901 134.391  72.492  1.00 38.65      B    C
ATOM   3602  CB  TYR B  34      66.709 133.217  71.949  1.00 39.87      B    C
ATOM   3603  CG  TYR B  34      66.110 131.861  72.247  1.00 39.26      B    C
ATOM   3604  CD1 TYR B  34      66.628 131.060  73.266  1.00 39.45      B    C
ATOM   3605  CE1 TYR B  34      66.124 129.781  73.513  1.00 37.93      B    C
ATOM   3606  CD2 TYR B  34      65.059 131.357  71.481  1.00 40.52      B    C
ATOM   3607  CE2 TYR B  34      64.548 130.085  71.714  1.00 40.09      B    C
ATOM   3608  CZ  TYR B  34      65.087 129.297  72.733  1.00 40.78      B    C
ATOM   3609  OH  TYR B  34      64.599 128.024  72.949  1.00 38.74      B    O
ATOM   3610  C   TYR B  34      66.811 135.608  72.648  1.00 38.39      B    C
ATOM   3611  O   TYR B  34      67.918 135.496  73.160  1.00 36.98      B    O
ATOM   3612  N   GLN B  35      66.339 136.765  72.193  1.00 36.97      B    N
ATOM   3613  CA  GLN B  35      67.079 138.016  72.285  1.00 37.14      B    C
ATOM   3614  CB  GLN B  35      67.507 138.291  73.731  1.00 38.45      B    C
ATOM   3615  CG  GLN B  35      66.404 138.183  74.775  1.00 38.16      B    C
ATOM   3616  CD  GLN B  35      65.114 138.859  74.347  1.00 39.93      B    C
ATOM   3617  OE1 GLN B  35      65.071 140.069  74.120  1.00 40.08      B    O
ATOM   3618  NE2 GLN B  35      64.051 138.069  74.226  1.00 39.21      B    N
ATOM   3619  C   GLN B  35      68.299 138.161  71.379  1.00 38.41      B    C
ATOM   3620  O   GLN B  35      69.271 138.803  71.758  1.00 39.85      B    O
ATOM   3621  N   TYR B  36      68.257 137.570  70.190  1.00 40.13      B    N
ATOM   3622  CA  TYR B  36      69.355 137.702  69.233  1.00 40.33      B    C
ATOM   3623  CB  TYR B  36      69.608 136.384  68.518  1.00 41.63      B    C
ATOM   3624  CG  TYR B  36      70.345 135.383  69.363  1.00 43.86      B    C
ATOM   3625  CD1 TYR B  36      71.669 135.062  69.093  1.00 42.52      B    C
ATOM   3626  CE1 TYR B  36      72.353 134.151  69.883  1.00 43.50      B    C
ATOM   3627  CD2 TYR B  36      69.724 134.768  70.447  1.00 43.74      B    C
ATOM   3628  CE2 TYR B  36      70.404 133.858  71.239  1.00 42.76      B    C
ATOM   3629  CZ  TYR B  36      71.712 133.555  70.949  1.00 41.04      B    C
ATOM   3630  OH  TYR B  36      72.378 132.637  71.707  1.00 40.50      B    O
ATOM   3631  C   TYR B  36      68.974 138.758  68.206  1.00 41.26      B    C
ATOM   3632  O   TYR B  36      67.818 138.832  67.788  1.00 41.62      B    O
ATOM   3633  N   GLN B  37      69.942 139.576  67.801  1.00 41.39      B    N
ATOM   3634  CA  GLN B  37      69.679 140.622  66.825  1.00 40.00      B    C
ATOM   3635  CB  GLN B  37      69.965 142.000  67.428  1.00 43.43      B    C
ATOM   3636  CG  GLN B  37      69.232 142.256  68.735  1.00 45.38      B    C
ATOM   3637  CD  GLN B  37      68.489 143.565  68.735  1.00 46.08      B    C
ATOM   3638  OE1 GLN B  37      69.081 144.630  68.615  1.00 47.91      B    O
ATOM   3639  NE2 GLN B  37      67.175 143.492  68.870  1.00 50.85      B    N
ATOM   3640  C   GLN B  37      70.536 140.404  65.597  1.00 39.54      B    C
ATOM   3641  O   GLN B  37      71.701 140.023  65.697  1.00 39.28      B    O
ATOM   3642  N   GLU B  38      69.954 140.659  64.432  1.00 39.60      B    N
ATOM   3643  CA  GLU B  38      70.657 140.457  63.182  1.00 37.32      B    C
ATOM   3644  CB  GLU B  38      69.687 140.483  61.987  1.00 36.73      B    C
ATOM   3645  CG  GLU B  38      70.406 140.252  60.656  1.00 39.01      B    C
ATOM   3646  CD  GLU B  38      69.484 140.177  59.444  1.00 39.98      B    C
ATOM   3647  OE1 GLU B  38      68.429 140.835  59.449  1.00 39.97      B    O
ATOM   3648  OE2 GLU B  38      69.834 139.479  58.469  1.00 41.19      B    O
ATOM   3649  C   GLU B  38      71.802 141.414  62.912  1.00 37.12      B    C
ATOM   3650  O   GLU B  38      71.780 142.600  63.263  1.00 34.84      B    O
ATOM   3651  N   ILE B  39      72.816 140.865  62.265  1.00 35.68      B    N
ATOM   3652  CA  ILE B  39      73.977 141.630  61.897  1.00 36.70      B    C
ATOM   3653  CB  ILE B  39      75.147 141.287  62.802  1.00 35.29      B    C
ATOM   3654  CG2 ILE B  39      75.443 139.795  62.726  1.00 40.43      B    C
ATOM   3655  CG1 ILE B  39      76.366 142.093  62.403  1.00 37.13      B    C
ATOM   3656  CD1 ILE B  39      77.517 141.880  63.354  1.00 41.30      B    C
ATOM   3657  C   ILE B  39      74.262 141.232  60.458  1.00 35.92      B    C
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FIGURE 11-70

ATOM	3658	O	ILE	B	39	74.238	140.045	60.114	1.00	34.86	B	O
ATOM	3659	N	ARG	B	40	74.483	142.224	59.605	1.00	34.95	B	N
ATOM	3660	CA	ARG	B	40	74.769	141.939	58.217	1.00	36.81	B	C
ATOM	3661	CB	ARG	B	40	73.672	142.501	57.308	1.00	37.88	B	C
ATOM	3662	CG	ARG	B	40	72.306	141.922	57.578	1.00	38.00	B	C
ATOM	3663	CD	ARG	B	40	71.256	142.510	56.661	1.00	38.12	B	C
ATOM	3664	NE	ARG	B	40	69.906	142.092	57.042	1.00	37.08	B	N
ATOM	3665	CZ	ARG	B	40	68.810	142.402	56.359	1.00	35.44	B	C
ATOM	3666	NH1	ARG	B	40	68.902	143.133	55.253	1.00	33.18	B	N
ATOM	3667	NH2	ARG	B	40	67.622	141.978	56.781	1.00	35.98	B	N
ATOM	3668	C	ARG	B	40	76.104	142.546	57.845	1.00	37.35	B	C
ATOM	3669	O	ARG	B	40	76.334	143.741	58.038	1.00	38.73	B	O
ATOM	3670	N	THR	B	41	76.990	141.711	57.324	1.00	37.92	B	N
ATOM	3671	CA	THR	B	41	78.302	142.174	56.898	1.00	38.52	B	C
ATOM	3672	CB	THR	B	41	79.420	141.286	57.475	1.00	38.06	B	C
ATOM	3673	OG1	THR	B	41	79.231	139.925	57.058	1.00	37.29	B	O
ATOM	3674	CG2	THR	B	41	79.392	141.347	58.988	1.00	36.32	B	C
ATOM	3675	C	THR	B	41	78.304	142.096	55.384	1.00	37.50	B	C
ATOM	3676	O	THR	B	41	77.456	141.429	54.802	1.00	37.11	B	O
ATOM	3677	N	PRO	B	42	79.244	142.783	54.726	1.00	39.02	B	N
ATOM	3678	CD	PRO	B	42	80.200	143.760	55.278	1.00	37.63	B	C
ATOM	3679	CA	PRO	B	42	79.304	142.756	53.258	1.00	39.15	B	C
ATOM	3680	CB	PRO	B	42	80.439	143.719	52.942	1.00	38.64	B	C
ATOM	3681	CG	PRO	B	42	80.414	144.684	54.105	1.00	38.63	B	C
ATOM	3682	C	PRO	B	42	79.564	141.364	52.685	1.00	42.12	B	C
ATOM	3683	O	PRO	B	42	80.135	140.498	53.348	1.00	42.56	B	O
ATOM	3684	N	ILE	B	43	79.122	141.148	51.454	1.00	45.66	B	N
ATOM	3685	CA	ILE	B	43	79.344	139.873	50.787	1.00	49.13	B	C
ATOM	3686	CB	ILE	B	43	78.656	139.831	49.408	1.00	49.53	B	C
ATOM	3687	CG2	ILE	B	43	78.991	138.533	48.707	1.00	50.93	B	C
ATOM	3688	CG1	ILE	B	43	77.141	140.013	49.566	1.00	47.56	B	C
ATOM	3689	CD1	ILE	B	43	76.484	138.964	50.403	1.00	44.35	B	C
ATOM	3690	C	ILE	B	43	80.850	139.757	50.590	1.00	51.35	B	C
ATOM	3691	O	ILE	B	43	81.412	138.670	50.634	1.00	51.70	B	O
ATOM	3692	N	PHE	B	44	81.500	140.894	50.369	1.00	56.27	B	N
ATOM	3693	CA	PHE	B	44	82.942	140.913	50.198	1.00	62.22	B	C
ATOM	3694	CB	PHE	B	44	83.332	141.820	49.039	1.00	64.85	B	C
ATOM	3695	CG	PHE	B	44	83.095	141.198	47.702	1.00	69.63	B	C
ATOM	3696	CD1	PHE	B	44	81.843	141.262	47.102	1.00	71.08	B	C
ATOM	3697	CD2	PHE	B	44	84.115	140.495	47.060	1.00	72.03	B	C
ATOM	3698	CE1	PHE	B	44	81.606	140.631	45.878	1.00	73.57	B	C
ATOM	3699	CE2	PHE	B	44	83.891	139.860	45.834	1.00	73.48	B	C
ATOM	3700	CZ	PHE	B	44	82.633	139.929	45.243	1.00	73.69	B	C
ATOM	3701	C	PHE	B	44	83.612	141.370	51.478	1.00	64.64	B	C
ATOM	3702	O	PHE	B	44	83.374	142.476	51.956	1.00	65.91	B	O
ATOM	3703	N	GLU	B	45	84.450	140.501	52.031	1.00	67.89	B	N
ATOM	3704	CA	GLU	B	45	85.145	140.780	53.279	1.00	71.76	B	C
ATOM	3705	CB	GLU	B	45	84.960	139.585	54.221	1.00	70.54	B	C
ATOM	3706	CG	GLU	B	45	85.375	139.839	55.655	1.00	71.65	B	C
ATOM	3707	CD	GLU	B	45	84.476	140.839	56.367	1.00	72.14	B	C
ATOM	3708	OE1	GLU	B	45	84.796	141.181	57.520	1.00	74.74	B	O
ATOM	3709	OE2	GLU	B	45	83.456	141.282	55.792	1.00	70.07	B	O
ATOM	3710	C	GLU	B	45	86.635	141.055	53.060	1.00	75.16	B	C
ATOM	3711	O	GLU	B	45	87.185	140.724	52.010	1.00	75.00	B	O
ATOM	3712	N	HIS	B	46	87.279	141.673	54.049	1.00	80.43	B	N
ATOM	3713	CA	HIS	B	46	88.711	141.967	53.970	1.00	85.56	B	C
ATOM	3714	CB	HIS	B	46	89.199	142.688	55.234	1.00	88.12	B	C
ATOM	3715	CG	HIS	B	46	88.700	144.093	55.379	1.00	91.13	B	C
ATOM	3716	CD2	HIS	B	46	88.002	144.691	56.376	1.00	92.15	B	C
ATOM	3717	ND1	HIS	B	46	88.959	145.078	54.449	1.00	91.82	B	N
ATOM	3718	CE1	HIS	B	46	88.443	146.221	54.867	1.00	92.65	B	C

FIGURE 11-71

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ATOM   3719  NE2 HIS B  46      87.858 146.014  56.034  1.00 93.14       B    N
ATOM   3720  C   HIS B  46      89.465 140.643  53.852  1.00 88.10       B    C
ATOM   3721  O   HIS B  46      89.232 139.716  54.634  1.00 87.88       B    O
ATOM   3722  N   TYR B  47      90.370 140.559  52.882  1.00 90.87       B    N
ATOM   3723  CA  TYR B  47      91.156 139.347  52.668  1.00 93.57       B    C
ATOM   3724  CB  TYR B  47      92.252 139.617  51.627  1.00 95.73       B    C
ATOM   3725  CG  TYR B  47      93.309 138.534  51.535  1.00 97.90       B    C
ATOM   3726  CD1 TYR B  47      92.989 137.249  51.096  1.00 98.53       B    C
ATOM   3727  CE1 TYR B  47      93.956 136.246  51.042  1.00 99.43       B    C
ATOM   3728  CD2 TYR B  47      94.627 138.792  51.917  1.00 99.02       B    C
ATOM   3729  CE2 TYR B  47      95.599 137.800  51.869  1.00 99.60       B    C
ATOM   3730  CZ  TYR B  47      95.260 136.530  51.432  1.00100.00       B    C
ATOM   3731  OH  TYR B  47      96.229 135.550  51.390  1.00100.00       B    O
ATOM   3732  C   TYR B  47      91.780 138.815  53.963  1.00 94.28       B    C
ATOM   3733  O   TYR B  47      91.694 137.619  54.258  1.00 94.11       B    O
ATOM   3734  N   GLU B  48      92.403 139.708  54.731  1.00 95.41       B    N
ATOM   3735  CA  GLU B  48      93.049 139.337  55.991  1.00 96.05       B    C
ATOM   3736  CB  GLU B  48      93.678 140.567  56.662  1.00 97.16       B    C
ATOM   3737  CG  GLU B  48      94.817 141.230  55.889  1.00 98.90       B    C
ATOM   3738  CD  GLU B  48      94.336 142.205  54.825  1.00 99.92       B    C
ATOM   3739  OE1 GLU B  48      93.740 141.762  53.819  1.00 99.70       B    O
ATOM   3740  OE2 GLU B  48      94.555 143.424  55.001  1.00100.00       B    O
ATOM   3741  C   GLU B  48      92.085 138.676  56.975  1.00 95.57       B    C
ATOM   3742  O   GLU B  48      92.383 137.618  57.530  1.00 95.94       B    O
ATOM   3743  N   VAL B  49      90.936 139.310  57.194  1.00 94.49       B    N
ATOM   3744  CA  VAL B  49      89.927 138.793  58.114  1.00 94.23       B    C
ATOM   3745  CB  VAL B  49      88.551 139.456  57.854  1.00 93.94       B    C
ATOM   3746  CG1 VAL B  49      87.476 138.791  58.707  1.00 92.62       B    C
ATOM   3747  CG2 VAL B  49      88.627 140.944  58.163  1.00 92.82       B    C
ATOM   3748  C   VAL B  49      89.758 137.274  58.028  1.00 94.19       B    C
ATOM   3749  O   VAL B  49      89.682 136.593  59.054  1.00 94.00       B    O
ATOM   3750  N   ILE B  50      89.700 136.755  56.804  1.00 93.93       B    N
ATOM   3751  CA  ILE B  50      89.530 135.321  56.571  1.00 93.80       B    C
ATOM   3752  CB  ILE B  50      89.494 135.012  55.048  1.00 93.12       B    C
ATOM   3753  CG2 ILE B  50      89.172 133.538  54.816  1.00 91.54       B    C
ATOM   3754  CG1 ILE B  50      88.451 135.904  54.360  1.00 92.30       B    C
ATOM   3755  CD1 ILE B  50      87.044 135.798  54.937  1.00 90.73       B    C
ATOM   3756  C   ILE B  50      90.634 134.489  57.238  1.00 94.39       B    C
ATOM   3757  O   ILE B  50      90.345 133.624  58.071  1.00 93.84       B    O
ATOM   3758  N   SER B  51      91.888 134.757  56.871  1.00 94.53       B    N
ATOM   3759  CA  SER B  51      93.046 134.052  57.432  1.00 95.15       B    C
ATOM   3760  CB  SER B  51      93.167 134.342  58.933  1.00 95.60       B    C
ATOM   3761  OG  SER B  51      93.332 135.727  59.186  1.00 96.13       B    O
ATOM   3762  C   SER B  51      93.015 132.535  57.216  1.00 95.67       B    C
ATOM   3763  O   SER B  51      93.920 132.026  56.518  1.00 95.72       B    O
ATOM   3764  OXT SER B  51      92.099 131.867  57.749  1.00 95.60       B    O
TER    3765      SER B  51                                               B
ATOM   3766  CB  ASP B  70      88.202 129.707  51.421  1.00 98.67       B    C
ATOM   3767  CG  ASP B  70      89.245 130.770  51.754  1.00 98.28       B    C
ATOM   3768  OD1 ASP B  70      88.875 131.957  51.875  1.00 97.53       B    O
ATOM   3769  OD2 ASP B  70      90.437 130.415  51.893  1.00 96.77       B    O
ATOM   3770  C   ASP B  70      88.591 130.166  48.995  1.00 99.95       B    C
ATOM   3771  O   ASP B  70      89.434 129.296  48.768  1.00100.00       B    O
ATOM   3772  N   ASP B  70      86.620 128.806  49.729  1.00 98.42       B    N
ATOM   3773  CA  ASP B  70      87.522 129.949  50.066  1.00 99.32       B    C
ATOM   3774  N   LYS B  71      88.542 131.333  48.351  1.00100.00       B    N
ATOM   3775  CA  LYS B  71      89.488 131.733  47.304  1.00100.00       B    C
ATOM   3776  CB  LYS B  71      89.808 130.563  46.359  1.00100.00       B    C
ATOM   3777  CG  LYS B  71      91.153 129.889  46.645  1.00 99.99       B    C
ATOM   3778  CD  LYS B  71      91.381 128.661  45.774  1.00 99.48       B    C
ATOM   3779  CE  LYS B  71      90.363 127.570  46.077  1.00 98.95       B    C
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FIGURE 11-72

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ATOM   3780  NZ  LYS B  71      90.615 126.333  45.286  1.00 98.69      B    N
ATOM   3781  C   LYS B  71      88.917 132.901  46.503  1.00100.00      B    C
ATOM   3782  O   LYS B  71      87.701 133.093  46.457  1.00100.00      B    O
ATOM   3783  N   GLY B  72      89.801 133.681  45.883  1.00100.00      B    N
ATOM   3784  CA  GLY B  72      89.366 134.825  45.098  1.00100.00      B    C
ATOM   3785  C   GLY B  72      90.456 135.853  44.829  1.00100.00      B    C
ATOM   3786  O   GLY B  72      91.388 135.592  44.062  1.00100.00      B    O
ATOM   3787  N   ASP B  73      90.340 137.021  45.464  1.00100.00      B    N
ATOM   3788  CA  ASP B  73      91.301 138.116  45.295  1.00100.00      B    C
ATOM   3789  CB  ASP B  73      90.557 139.449  45.098  1.00100.00      B    C
ATOM   3790  CG  ASP B  73      89.699 139.472  43.843  1.00100.00      B    C
ATOM   3791  OD1 ASP B  73      90.265 139.373  42.734  1.00100.00      B    O
ATOM   3792  OD2 ASP B  73      88.459 139.597  43.966  1.00100.00      B    O
ATOM   3793  C   ASP B  73      92.259 138.268  46.484  1.00100.00      B    C
ATOM   3794  O   ASP B  73      92.402 137.361  47.308  1.00100.00      B    O
ATOM   3795  N   ARG B  74      92.910 139.431  46.549  1.00100.00      B    N
ATOM   3796  CA  ARG B  74      93.845 139.769  47.624  1.00 99.63      B    C
ATOM   3797  CB  ARG B  74      95.277 139.918  47.083  1.00100.00      B    C
ATOM   3798  CG  ARG B  74      95.776 141.359  46.984  1.00 99.85      B    C
ATOM   3799  CD  ARG B  74      97.268 141.415  46.689  1.00 99.71      B    C
ATOM   3800  NE  ARG B  74      97.795 142.779  46.738  1.00100.00      B    N
ATOM   3801  CZ  ARG B  74      97.428 143.762  45.916  1.00100.00      B    C
ATOM   3802  NH1 ARG B  74      97.969 144.969  46.041  1.00 99.53      B    N
ATOM   3803  NH2 ARG B  74      96.523 143.542  44.967  1.00100.00      B    N
ATOM   3804  C   ARG B  74      93.384 141.089  48.253  1.00 98.72      B    C
ATOM   3805  O   ARG B  74      93.637 141.351  49.432  1.00 98.35      B    O
ATOM   3806  N   HIS B  75      92.724 141.919  47.445  1.00 97.93      B    N
ATOM   3807  CA  HIS B  75      92.185 143.200  47.905  1.00 96.85      B    C
ATOM   3808  CB  HIS B  75      91.672 144.038  46.720  1.00 98.10      B    C
ATOM   3809  CG  HIS B  75      92.727 144.863  46.044  1.00 99.70      B    C
ATOM   3810  CD2 HIS B  75      93.164 144.874  44.761  1.00100.00      B    C
ATOM   3811  ND1 HIS B  75      93.435 145.851  46.696  1.00100.00      B    N
ATOM   3812  CE1 HIS B  75      94.260 146.435  45.846  1.00100.00      B    C
ATOM   3813  NE2 HIS B  75      94.115 145.861  44.664  1.00100.00      B    N
ATOM   3814  C   HIS B  75      91.014 142.880  48.835  1.00 94.76      B    C
ATOM   3815  O   HIS B  75      91.016 143.246  50.010  1.00 95.29      B    O
ATOM   3816  N   VAL B  76      90.018 142.188  48.284  1.00 91.72      B    N
ATOM   3817  CA  VAL B  76      88.824 141.780  49.023  1.00 88.36      B    C
ATOM   3818  CB  VAL B  76      87.663 142.787  48.829  1.00 88.91      B    C
ATOM   3819  CG1 VAL B  76      86.567 142.514  49.840  1.00 88.93      B    C
ATOM   3820  CG2 VAL B  76      88.172 144.214  48.965  1.00 89.60      B    C
ATOM   3821  C   VAL B  76      88.398 140.427  48.453  1.00 85.46      B    C
ATOM   3822  O   VAL B  76      88.726 140.113  47.308  1.00 85.12      B    O
ATOM   3823  N   THR B  77      87.674 139.628  49.235  1.00 82.01      B    N
ATOM   3824  CA  THR B  77      87.237 138.313  48.762  1.00 79.07      B    C
ATOM   3825  CB  THR B  77      88.239 137.211  49.173  1.00 79.46      B    C
ATOM   3826  OG1 THR B  77      89.525 137.495  48.610  1.00 80.63      B    O
ATOM   3827  CG2 THR B  77      87.767 135.849  48.678  1.00 79.41      B    C
ATOM   3828  C   THR B  77      85.862 137.889  49.265  1.00 76.15      B    C
ATOM   3829  O   THR B  77      85.446 138.260  50.358  1.00 75.45      B    O
ATOM   3830  N   LEU B  78      85.163 137.100  48.456  1.00 73.23      B    N
ATOM   3831  CA  LEU B  78      83.846 136.604  48.830  1.00 70.68      B    C
ATOM   3832  CB  LEU B  78      83.294 135.693  47.731  1.00 71.04      B    C
ATOM   3833  CG  LEU B  78      82.883 136.408  46.441  1.00 71.77      B    C
ATOM   3834  CD1 LEU B  78      82.607 135.387  45.341  1.00 71.48      B    C
ATOM   3835  CD2 LEU B  78      81.649 137.269  46.708  1.00 72.36      B    C
ATOM   3836  C   LEU B  78      83.959 135.836  50.141  1.00 67.98      B    C
ATOM   3837  O   LEU B  78      84.817 134.969  50.291  1.00 67.45      B    O
ATOM   3838  N   ARG B  79      83.089 136.164  51.089  1.00 66.02      B    N
ATOM   3839  CA  ARG B  79      83.107 135.516  52.394  1.00 63.95      B    C
ATOM   3840  CB  ARG B  79      82.136 136.221  53.353  1.00 63.98      B    C
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FIGURE 11-73

ATOM	3841	CG	ARG	B	79	80.669	136.110	52.963	1.00	62.44	B	C
ATOM	3842	CD	ARG	B	79	79.767	136.957	53.861	1.00	62.22	B	C
ATOM	3843	NE	ARG	B	79	78.352	136.788	53.524	1.00	59.93	B	N
ATOM	3844	CZ	ARG	B	79	77.398	137.660	53.838	1.00	58.06	B	C
ATOM	3845	NH1	ARG	B	79	77.704	138.769	54.498	1.00	56.37	B	N
ATOM	3846	NH2	ARG	B	79	76.139	137.424	53.487	1.00	54.80	B	N
ATOM	3847	C	ARG	B	79	82.763	134.035	52.313	1.00	61.90	B	C
ATOM	3848	O	ARG	B	79	81.730	133.650	51.768	1.00	59.93	B	O
ATOM	3849	N	PRO	B	80	83.647	133.178	52.835	1.00	60.78	B	N
ATOM	3850	CD	PRO	B	80	85.052	133.446	53.193	1.00	60.27	B	C
ATOM	3851	CA	PRO	B	80	83.379	131.739	52.801	1.00	60.19	B	C
ATOM	3852	CB	PRO	B	80	84.768	131.124	52.951	1.00	60.52	B	C
ATOM	3853	CG	PRO	B	80	85.490	132.130	53.795	1.00	60.20	B	C
ATOM	3854	C	PRO	B	80	82.451	131.342	53.938	1.00	59.13	B	C
ATOM	3855	O	PRO	B	80	81.785	130.310	53.880	1.00	59.24	B	O
ATOM	3856	N	GLU	B	81	82.406	132.181	54.967	1.00	57.59	B	N
ATOM	3857	CA	GLU	B	81	81.579	131.914	56.136	1.00	56.30	B	C
ATOM	3858	CB	GLU	B	81	82.370	131.081	57.133	1.00	57.60	B	C
ATOM	3859	CG	GLU	B	81	83.725	131.677	57.453	1.00	60.47	B	C
ATOM	3860	CD	GLU	B	81	84.215	131.259	58.814	1.00	63.05	B	C
ATOM	3861	OE1	GLU	B	81	84.119	130.053	59.128	1.00	64.42	B	O
ATOM	3862	OE2	GLU	B	81	84.694	132.132	59.569	1.00	65.53	B	O
ATOM	3863	C	GLU	B	81	81.117	133.212	56.799	1.00	53.75	B	C
ATOM	3864	O	GLU	B	81	81.443	134.296	56.330	1.00	54.57	B	O
ATOM	3865	N	GLY	B	82	80.364	133.094	57.891	1.00	51.84	B	N
ATOM	3866	CA	GLY	B	82	79.849	134.271	58.571	1.00	50.04	B	C
ATOM	3867	C	GLY	B	82	80.447	134.607	59.931	1.00	47.49	B	C
ATOM	3868	O	GLY	B	82	80.377	135.758	60.363	1.00	49.58	B	O
ATOM	3869	N	THR	B	83	81.030	133.624	60.607	1.00	45.81	B	N
ATOM	3870	CA	THR	B	83	81.625	133.864	61.916	1.00	43.31	B	C
ATOM	3871	CB	THR	B	83	82.159	132.549	62.539	1.00	44.70	B	C
ATOM	3872	OG1	THR	B	83	81.106	131.578	62.570	1.00	44.67	B	O
ATOM	3873	CG2	THR	B	83	82.631	132.776	63.972	1.00	43.25	B	C
ATOM	3874	C	THR	B	83	82.750	134.898	61.828	1.00	43.33	B	C
ATOM	3875	O	THR	B	83	82.660	135.958	62.455	1.00	42.71	B	O
ATOM	3876	N	ALA	B	84	83.791	134.619	61.044	1.00	40.93	B	N
ATOM	3877	CA	ALA	B	84	84.905	135.563	60.912	1.00	41.24	B	C
ATOM	3878	CB	ALA	B	84	85.870	135.123	59.792	1.00	40.63	B	C
ATOM	3879	C	ALA	B	84	84.418	136.988	60.647	1.00	40.11	B	C
ATOM	3880	O	ALA	B	84	84.848	137.933	61.310	1.00	42.44	B	O
ATOM	3881	N	PRO	B	85	83.528	137.167	59.661	1.00	38.25	B	N
ATOM	3882	CD	PRO	B	85	83.059	136.202	58.651	1.00	37.44	B	C
ATOM	3883	CA	PRO	B	85	83.023	138.510	59.369	1.00	35.84	B	C
ATOM	3884	CB	PRO	B	85	82.085	138.279	58.187	1.00	35.16	B	C
ATOM	3885	CG	PRO	B	85	82.707	137.107	57.494	1.00	35.26	B	C
ATOM	3886	C	PRO	B	85	82.274	139.073	60.570	1.00	34.51	B	C
ATOM	3887	O	PRO	B	85	82.295	140.264	60.826	1.00	33.80	B	O
ATOM	3888	N	ILE	B	86	81.605	138.216	61.321	1.00	34.43	B	N
ATOM	3889	CA	ILE	B	86	80.866	138.726	62.450	1.00	36.14	B	C
ATOM	3890	CB	ILE	B	86	79.751	137.749	62.848	1.00	37.02	B	C
ATOM	3891	CG2	ILE	B	86	79.309	137.989	64.286	1.00	33.60	B	C
ATOM	3892	CG1	ILE	B	86	78.595	137.930	61.854	1.00	36.28	B	C
ATOM	3893	CD1	ILE	B	86	77.450	137.030	62.093	1.00	39.59	B	C
ATOM	3894	C	ILE	B	86	81.753	139.088	63.622	1.00	36.54	B	C
ATOM	3895	O	ILE	B	86	81.466	140.050	64.339	1.00	36.91	B	O
ATOM	3896	N	VAL	B	87	82.839	138.346	63.805	1.00	35.46	B	N
ATOM	3897	CA	VAL	B	87	83.763	138.638	64.891	1.00	36.32	B	C
ATOM	3898	CB	VAL	B	87	84.821	137.536	65.045	1.00	37.83	B	C
ATOM	3899	CG1	VAL	B	87	85.861	137.964	66.073	1.00	39.29	B	C
ATOM	3900	CG2	VAL	B	87	84.153	136.225	65.477	1.00	36.37	B	C
ATOM	3901	C	VAL	B	87	84.453	139.940	64.527	1.00	36.66	B	C

FIGURE 11-74

ATOM	3902	O	VAL	B	87	84.677	140.813	65.373	1.00	37.75	B	O
ATOM	3903	N	ARG	B	88	84.753	140.082	63.243	1.00	35.47	B	N
ATOM	3904	CA	ARG	B	88	85.410	141.285	62.760	1.00	35.34	B	C
ATOM	3905	CB	ARG	B	88	85.711	141.134	61.271	1.00	36.76	B	C
ATOM	3906	CG	ARG	B	88	86.601	142.212	60.674	1.00	39.53	B	C
ATOM	3907	CD	ARG	B	88	85.966	142.785	59.414	1.00	40.93	B	C
ATOM	3908	NE	ARG	B	88	85.038	143.844	59.768	1.00	44.41	B	N
ATOM	3909	CZ	ARG	B	88	83.771	143.916	59.392	1.00	42.08	B	C
ATOM	3910	NH1	ARG	B	88	83.233	142.981	58.624	1.00	39.51	B	N
ATOM	3911	NH2	ARG	B	88	83.042	144.937	59.810	1.00	42.72	B	N
ATOM	3912	C	ARG	B	88	84.527	142.513	63.004	1.00	35.84	B	C
ATOM	3913	O	ARG	B	88	84.999	143.531	63.509	1.00	36.23	B	O
ATOM	3914	N	ALA	B	89	83.246	142.422	62.650	1.00	33.60	B	N
ATOM	3915	CA	ALA	B	89	82.342	143.549	62.852	1.00	33.77	B	C
ATOM	3916	CB	ALA	B	89	80.985	143.262	62.205	1.00	34.41	B	C
ATOM	3917	C	ALA	B	89	82.178	143.833	64.351	1.00	33.42	B	C
ATOM	3918	O	ALA	B	89	82.017	144.981	64.765	1.00	35.60	B	O
ATOM	3919	N	PHE	B	90	82.231	142.777	65.153	1.00	33.91	B	N
ATOM	3920	CA	PHE	B	90	82.113	142.879	66.604	1.00	33.04	B	C
ATOM	3921	CB	PHE	B	90	82.117	141.469	67.201	1.00	31.99	B	C
ATOM	3922	CG	PHE	B	90	82.091	141.433	68.707	1.00	32.81	B	C
ATOM	3923	CD1	PHE	B	90	80.918	141.692	69.407	1.00	31.25	B	C
ATOM	3924	CD2	PHE	B	90	83.238	141.098	69.422	1.00	31.99	B	C
ATOM	3925	CE1	PHE	B	90	80.892	141.612	70.804	1.00	31.58	B	C
ATOM	3926	CE2	PHE	B	90	83.220	141.014	70.814	1.00	32.00	B	C
ATOM	3927	CZ	PHE	B	90	82.051	141.268	71.507	1.00	28.24	B	C
ATOM	3928	C	PHE	B	90	83.289	143.695	67.155	1.00	33.50	B	C
ATOM	3929	O	PHE	B	90	83.094	144.635	67.927	1.00	32.15	B	O
ATOM	3930	N	VAL	B	91	84.503	143.333	66.738	1.00	35.16	B	N
ATOM	3931	CA	VAL	B	91	85.732	144.014	67.161	1.00	34.89	B	C
ATOM	3932	CB	VAL	B	91	86.980	143.238	66.667	1.00	34.31	B	C
ATOM	3933	CG1	VAL	B	91	88.256	143.998	67.019	1.00	32.33	B	C
ATOM	3934	CG2	VAL	B	91	87.009	141.846	67.285	1.00	33.66	B	C
ATOM	3935	C	VAL	B	91	85.832	145.454	66.629	1.00	37.76	B	C
ATOM	3936	O	VAL	B	91	86.092	146.407	67.369	1.00	37.82	B	O
ATOM	3937	N	GLU	B	92	85.630	145.590	65.327	1.00	38.23	B	N
ATOM	3938	CA	GLU	B	92	85.701	146.863	64.634	1.00	37.08	B	C
ATOM	3939	CB	GLU	B	92	85.494	146.583	63.142	1.00	41.38	B	C
ATOM	3940	CG	GLU	B	92	85.559	147.757	62.199	1.00	45.16	B	C
ATOM	3941	CD	GLU	B	92	85.818	147.295	60.761	1.00	48.44	B	C
ATOM	3942	OE1	GLU	B	92	85.402	148.000	59.821	1.00	50.05	B	O
ATOM	3943	OE2	GLU	B	92	86.452	146.229	60.575	1.00	48.03	B	O
ATOM	3944	C	GLU	B	92	84.687	147.876	65.156	1.00	36.14	B	C
ATOM	3945	O	GLU	B	92	84.934	149.082	65.162	1.00	33.34	B	O
ATOM	3946	N	ASN	B	93	83.533	147.400	65.599	1.00	36.05	B	N
ATOM	3947	CA	ASN	B	93	82.543	148.333	66.113	1.00	36.80	B	C
ATOM	3948	CB	ASN	B	93	81.169	147.973	65.582	1.00	35.11	B	C
ATOM	3949	CG	ASN	B	93	81.050	148.289	64.118	1.00	37.45	B	C
ATOM	3950	OD1	ASN	B	93	80.927	149.454	63.739	1.00	37.43	B	O
ATOM	3951	ND2	ASN	B	93	81.134	147.260	63.275	1.00	36.46	B	N
ATOM	3952	C	ASN	B	93	82.555	148.428	67.621	1.00	36.49	B	C
ATOM	3953	O	ASN	B	93	81.762	149.169	68.205	1.00	35.81	B	O
ATOM	3954	N	LYS	B	94	83.481	147.682	68.227	1.00	36.15	B	N
ATOM	3955	CA	LYS	B	94	83.678	147.659	69.672	1.00	37.92	B	C
ATOM	3956	CB	LYS	B	94	84.163	149.028	70.155	1.00	39.34	B	C
ATOM	3957	CG	LYS	B	94	85.491	149.471	69.565	1.00	40.70	B	C
ATOM	3958	CD	LYS	B	94	85.612	150.990	69.580	1.00	45.80	B	C
ATOM	3959	CE	LYS	B	94	87.008	151.453	69.164	1.00	47.75	B	C
ATOM	3960	NZ	LYS	B	94	87.427	150.903	67.841	1.00	49.75	B	N
ATOM	3961	C	LYS	B	94	82.408	147.283	70.406	1.00	39.29	B	C
ATOM	3962	O	LYS	B	94	82.132	147.815	71.478	1.00	40.90	B	O

FIGURE 11-75

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ATOM   3963  N   LEU B  95      81.658 146.343  69.832  1.00 39.64      B    N
ATOM   3964  CA  LEU B  95      80.406 145.875  70.408  1.00 36.49      B    C
ATOM   3965  CB  LEU B  95      79.664 145.022  69.385  1.00 37.41      B    C
ATOM   3966  CG  LEU B  95      79.480 145.754  68.054  1.00 36.92      B    C
ATOM   3967  CD1 LEU B  95      78.678 144.892  67.088  1.00 38.88      B    C
ATOM   3968  CD2 LEU B  95      78.771 147.055  68.301  1.00 36.33      B    C
ATOM   3969  C   LEU B  95      80.601 145.094  71.698  1.00 36.28      B    C
ATOM   3970  O   LEU B  95      79.634 144.591  72.285  1.00 33.04      B    O
ATOM   3971  N   TYR B  96      81.854 144.977  72.129  1.00 34.16      B    N
ATOM   3972  CA  TYR B  96      82.164 144.295  73.379  1.00 35.23      B    C
ATOM   3973  CB  TYR B  96      83.531 143.606  73.297  1.00 35.13      B    C
ATOM   3974  CG  TYR B  96      84.660 144.525  72.883  1.00 35.94      B    C
ATOM   3975  CD1 TYR B  96      85.150 145.504  73.752  1.00 36.45      B    C
ATOM   3976  CE1 TYR B  96      86.148 146.389  73.349  1.00 36.12      B    C
ATOM   3977  CD2 TYR B  96      85.200 144.455  71.602  1.00 34.35      B    C
ATOM   3978  CE2 TYR B  96      86.194 145.338  71.191  1.00 36.57      B    C
ATOM   3979  CZ  TYR B  96      86.665 146.300  72.067  1.00 35.56      B    C
ATOM   3980  OH  TYR B  96      87.648 147.173  71.656  1.00 37.89      B    O
ATOM   3981  C   TYR B  96      82.190 145.346  74.485  1.00 37.49      B    C
ATOM   3982  O   TYR B  96      82.151 145.019  75.674  1.00 38.58      B    O
ATOM   3983  N   GLY B  97      82.235 146.610  74.070  1.00 38.85      B    N
ATOM   3984  CA  GLY B  97      82.321 147.719  75.005  1.00 41.28      B    C
ATOM   3985  C   GLY B  97      81.198 147.984  75.988  1.00 43.67      B    C
ATOM   3986  O   GLY B  97      80.146 147.342  75.960  1.00 43.88      B    O
ATOM   3987  N   PRO B  98      81.416 148.940  76.900  1.00 45.67      B    N
ATOM   3988  CD  PRO B  98      82.662 149.715  77.061  1.00 45.53      B    C
ATOM   3989  CA  PRO B  98      80.426 149.318  77.912  1.00 45.79      B    C
ATOM   3990  CB  PRO B  98      81.118 150.446  78.667  1.00 45.43      B    C
ATOM   3991  CG  PRO B  98      82.592 150.127  78.507  1.00 45.71      B    C
ATOM   3992  C   PRO B  98      79.198 149.826  77.183  1.00 48.37      B    C
ATOM   3993  O   PRO B  98      79.338 150.537  76.188  1.00 49.29      B    O
ATOM   3994  N   GLU B  99      78.010 149.468  77.673  1.00 49.70      B    N
ATOM   3995  CA  GLU B  99      76.739 149.895  77.077  1.00 51.70      B    C
ATOM   3996  CB  GLU B  99      76.916 151.186  76.241  1.00 58.99      B    C
ATOM   3997  CG  GLU B  99      75.608 151.848  75.739  1.00 66.78      B    C
ATOM   3998  CD  GLU B  99      75.321 151.595  74.255  1.00 70.27      B    C
ATOM   3999  OE1 GLU B  99      75.250 150.413  73.845  1.00 71.95      B    O
ATOM   4000  OE2 GLU B  99      75.157 152.583  73.500  1.00 71.91      B    O
ATOM   4001  C   GLU B  99      76.124 148.816  76.203  1.00 48.60      B    C
ATOM   4002  O   GLU B  99      74.917 148.822  75.966  1.00 49.33      B    O
ATOM   4003  N   TYR B 100      76.945 147.891  75.719  1.00 44.46      B    N
ATOM   4004  CA  TYR B 100      76.432 146.827  74.870  1.00 41.82      B    C
ATOM   4005  CB  TYR B 100      77.461 146.465  73.797  1.00 40.75      B    C
ATOM   4006  CG  TYR B 100      77.656 147.580  72.793  1.00 39.52      B    C
ATOM   4007  CD1 TYR B 100      78.698 148.493  72.926  1.00 37.95      B    C
ATOM   4008  CE1 TYR B 100      78.845 149.561  72.037  1.00 40.38      B    C
ATOM   4009  CD2 TYR B 100      76.757 147.753  71.739  1.00 40.75      B    C
ATOM   4010  CE2 TYR B 100      76.893 148.820  70.835  1.00 42.33      B    C
ATOM   4011  CZ  TYR B 100      77.941 149.719  70.991  1.00 41.90      B    C
ATOM   4012  OH  TYR B 100      78.092 150.760  70.092  1.00 41.42      B    O
ATOM   4013  C   TYR B 100      76.039 145.602  75.670  1.00 40.69      B    C
ATOM   4014  O   TYR B 100      76.669 145.275  76.674  1.00 40.74      B    O
ATOM   4015  N   THR B 101      74.979 144.936  75.230  1.00 38.66      B    N
ATOM   4016  CA  THR B 101      74.493 143.749  75.912  1.00 39.87      B    C
ATOM   4017  CB  THR B 101      73.289 143.104  75.156  1.00 42.67      B    C
ATOM   4018  OG1 THR B 101      73.718 142.651  73.860  1.00 47.96      B    O
ATOM   4019  CG2 THR B 101      72.167 144.119  74.965  1.00 42.55      B    C
ATOM   4020  C   THR B 101      75.578 142.689  76.073  1.00 39.75      B    C
ATOM   4021  O   THR B 101      76.418 142.489  75.195  1.00 39.88      B    O
ATOM   4022  N   LYS B 102      75.555 142.033  77.225  1.00 39.27      B    N
ATOM   4023  CA  LYS B 102      76.472 140.950  77.554  1.00 37.66      B    C
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FIGURE 11-76

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ATOM   4024  CB  LYS B 102      77.374 141.341  78.735  1.00 37.30      B    C
ATOM   4025  CG  LYS B 102      78.184 142.631  78.590  1.00 36.96      B    C
ATOM   4026  CD  LYS B 102      79.427 142.428  77.731  1.00 37.97      B    C
ATOM   4027  CE  LYS B 102      80.342 143.645  77.748  1.00 31.85      B    C
ATOM   4028  NZ  LYS B 102      79.735 144.825  77.080  1.00 32.33      B    N
ATOM   4029  C   LYS B 102      75.525 139.827  78.004  1.00 37.23      B    C
ATOM   4030  O   LYS B 102      74.759 140.015  78.939  1.00 40.29      B    O
ATOM   4031  N   PRO B 103      75.515 138.675  77.314  1.00 36.05      B    N
ATOM   4032  CD  PRO B 103      74.721 137.523  77.777  1.00 36.10      B    C
ATOM   4033  CA  PRO B 103      76.307 138.316  76.134  1.00 35.43      B    C
ATOM   4034  CB  PRO B 103      76.136 136.803  76.060  1.00 36.63      B    C
ATOM   4035  CG  PRO B 103      74.756 136.593  76.589  1.00 35.24      B    C
ATOM   4036  C   PRO B 103      75.727 139.030  74.905  1.00 34.93      B    C
ATOM   4037  O   PRO B 103      74.532 139.324  74.857  1.00 32.94      B    O
ATOM   4038  N   TYR B 104      76.575 139.334  73.932  1.00 33.48      B    N
ATOM   4039  CA  TYR B 104      76.111 140.010  72.735  1.00 32.26      B    C
ATOM   4040  CB  TYR B 104      77.255 140.811  72.103  1.00 31.07      B    C
ATOM   4041  CG  TYR B 104      76.780 141.844  71.098  1.00 31.64      B    C
ATOM   4042  CD1 TYR B 104      76.268 143.076  71.518  1.00 31.00      B    C
ATOM   4043  CE1 TYR B 104      75.799 144.009  70.595  1.00 32.36      B    C
ATOM   4044  CD2 TYR B 104      76.809 141.573  69.734  1.00 27.93      B    C
ATOM   4045  CE2 TYR B 104      76.345 142.494  68.808  1.00 28.69      B    C
ATOM   4046  CZ  TYR B 104      75.844 143.704  69.229  1.00 31.30      B    C
ATOM   4047  OH  TYR B 104      75.410 144.616  68.284  1.00 29.26      B    O
ATOM   4048  C   TYR B 104      75.601 138.933  71.780  1.00 32.76      B    C
ATOM   4049  O   TYR B 104      76.380 138.202  71.170  1.00 34.35      B    O
ATOM   4050  N   LYS B 105      74.283 138.841  71.661  1.00 33.99      B    N
ATOM   4051  CA  LYS B 105      73.650 137.837  70.815  1.00 35.29      B    C
ATOM   4052  CB  LYS B 105      72.362 137.361  71.474  1.00 37.61      B    C
ATOM   4053  CG  LYS B 105      72.579 136.673  72.811  1.00 37.90      B    C
ATOM   4054  CD  LYS B 105      71.256 136.196  73.387  1.00 41.87      B    C
ATOM   4055  CE  LYS B 105      71.481 135.199  74.505  1.00 43.74      B    C
ATOM   4056  NZ  LYS B 105      70.196 134.768  75.105  1.00 46.09      B    N
ATOM   4057  C   LYS B 105      73.358 138.343  69.412  1.00 35.21      B    C
ATOM   4058  O   LYS B 105      72.591 139.291  69.229  1.00 37.36      B    O
ATOM   4059  N   THR B 106      73.962 137.693  68.423  1.00 33.47      B    N
ATOM   4060  CA  THR B 106      73.791 138.093  67.040  1.00 35.77      B    C
ATOM   4061  CB  THR B 106      75.042 138.803  66.496  1.00 37.38      B    C
ATOM   4062  OG1 THR B 106      76.137 137.874  66.436  1.00 40.30      B    O
ATOM   4063  CG2 THR B 106      75.419 139.933  67.380  1.00 35.86      B    C
ATOM   4064  C   THR B 106      73.538 136.921  66.121  1.00 34.60      B    C
ATOM   4065  O   THR B 106      74.034 135.825  66.334  1.00 36.86      B    O
ATOM   4066  N   TYR B 107      72.768 137.162  65.076  1.00 35.66      B    N
ATOM   4067  CA  TYR B 107      72.505 136.109  64.129  1.00 36.11      B    C
ATOM   4068  CB  TYR B 107      71.117 135.524  64.361  1.00 32.19      B    C
ATOM   4069  CG  TYR B 107      69.980 136.331  63.808  1.00 35.06      B    C
ATOM   4070  CD1 TYR B 107      69.644 136.267  62.447  1.00 34.84      B    C
ATOM   4071  CE1 TYR B 107      68.549 136.962  61.947  1.00 33.60      B    C
ATOM   4072  CD2 TYR B 107      69.197 137.116  64.645  1.00 35.27      B    C
ATOM   4073  CE2 TYR B 107      68.107 137.814  64.157  1.00 35.53      B    C
ATOM   4074  CZ  TYR B 107      67.784 137.734  62.812  1.00 35.92      B    C
ATOM   4075  OH  TYR B 107      66.696 138.432  62.349  1.00 37.70      B    O
ATOM   4076  C   TYR B 107      72.644 136.687  62.733  1.00 37.34      B    C
ATOM   4077  O   TYR B 107      72.453 137.878  62.527  1.00 36.74      B    O
ATOM   4078  N   TYR B 108      73.011 135.839  61.784  1.00 39.17      B    N
ATOM   4079  CA  TYR B 108      73.172 136.267  60.409  1.00 40.64      B    C
ATOM   4080  CB  TYR B 108      74.646 136.311  60.014  1.00 39.81      B    C
ATOM   4081  CG  TYR B 108      75.358 134.989  60.184  1.00 44.13      B    C
ATOM   4082  CD1 TYR B 108      75.805 134.573  61.432  1.00 45.65      B    C
ATOM   4083  CE1 TYR B 108      76.465 133.359  61.596  1.00 47.35      B    C
ATOM   4084  CD2 TYR B 108      75.582 134.149  59.095  1.00 45.51      B    C
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FIGURE 11-77

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ATOM   4085  CE2 TYR B 108      76.235 132.932  59.246  1.00 46.72      B    C
ATOM   4086  CZ  TYR B 108      76.678 132.542  60.500  1.00 48.50      B    C
ATOM   4087  OH  TYR B 108      77.344 131.340  60.660  1.00 50.54      B    O
ATOM   4088  C   TYR B 108      72.466 135.274  59.520  1.00 41.01      B    C
ATOM   4089  O   TYR B 108      72.065 134.201  59.962  1.00 41.26      B    O
ATOM   4090  N   MET B 109      72.314 135.653  58.264  1.00 40.28      B    N
ATOM   4091  CA  MET B 109      71.683 134.821  57.254  1.00 41.39      B    C
ATOM   4092  CB  MET B 109      70.163 134.906  57.291  1.00 39.60      B    C
ATOM   4093  CG  MET B 109      69.493 134.372  58.520  1.00 45.08      B    C
ATOM   4094  SD  MET B 109      67.671 134.367  58.330  1.00 51.80      B    S
ATOM   4095  CE  MET B 109      67.453 135.541  57.009  1.00 46.71      B    C
ATOM   4096  C   MET B 109      72.157 135.472  55.978  1.00 41.54      B    C
ATOM   4097  O   MET B 109      71.960 136.671  55.793  1.00 44.10      B    O
ATOM   4098  N   GLY B 110      72.795 134.702  55.109  1.00 41.10      B    N
ATOM   4099  CA  GLY B 110      73.270 135.271  53.872  1.00 40.44      B    C
ATOM   4100  C   GLY B 110      74.070 134.274  53.081  1.00 41.60      B    C
ATOM   4101  O   GLY B 110      74.522 133.260  53.620  1.00 40.33      B    O
ATOM   4102  N   PRO B 111      74.263 134.537  51.785  1.00 41.24      B    N
ATOM   4103  CD  PRO B 111      73.878 135.761  51.062  1.00 39.91      B    C
ATOM   4104  CA  PRO B 111      75.026 133.639  50.924  1.00 41.42      B    C
ATOM   4105  CB  PRO B 111      74.869 134.277  49.551  1.00 42.40      B    C
ATOM   4106  CG  PRO B 111      74.828 135.748  49.887  1.00 41.58      B    C
ATOM   4107  C   PRO B 111      76.488 133.565  51.335  1.00 42.00      B    C
ATOM   4108  O   PRO B 111      77.044 134.546  51.815  1.00 40.24      B    O
ATOM   4109  N   MET B 112      77.089 132.391  51.146  1.00 44.25      B    N
ATOM   4110  CA  MET B 112      78.506 132.163  51.426  1.00 46.44      B    C
ATOM   4111  CB  MET B 112      78.696 131.216  52.613  1.00 46.95      B    C
ATOM   4112  CG  MET B 112      78.142 131.736  53.945  1.00 49.46      B    C
ATOM   4113  SD  MET B 112      78.820 133.328  54.521  1.00 49.32      B    S
ATOM   4114  CE  MET B 112      77.529 133.824  55.652  1.00 51.34      B    C
ATOM   4115  C   MET B 112      79.098 131.538  50.158  1.00 48.32      B    C
ATOM   4116  O   MET B 112      78.384 130.908  49.371  1.00 46.69      B    O
ATOM   4117  N   PHE B 113      80.400 131.712  49.964  1.00 49.99      B    N
ATOM   4118  CA  PHE B 113      81.077 131.197  48.783  1.00 50.68      B    C
ATOM   4119  CB  PHE B 113      81.546 132.381  47.942  1.00 50.00      B    C
ATOM   4120  CG  PHE B 113      80.422 133.295  47.539  1.00 50.51      B    C
ATOM   4121  CD1 PHE B 113      79.569 132.952  46.489  1.00 50.24      B    C
ATOM   4122  CD2 PHE B 113      80.157 134.455  48.264  1.00 50.75      B    C
ATOM   4123  CE1 PHE B 113      78.465 133.745  46.169  1.00 48.91      B    C
ATOM   4124  CE2 PHE B 113      79.056 135.254  47.953  1.00 51.42      B    C
ATOM   4125  CZ  PHE B 113      78.206 134.897  46.902  1.00 50.55      B    C
ATOM   4126  C   PHE B 113      82.235 130.285  49.151  1.00 52.66      B    C
ATOM   4127  O   PHE B 113      83.205 130.718  49.776  1.00 53.93      B    O
ATOM   4128  N   ARG B 114      82.117 129.017  48.757  1.00 54.82      B    N
ATOM   4129  CA  ARG B 114      83.123 128.000  49.055  1.00 57.13      B    C
ATOM   4130  CB  ARG B 114      82.768 127.292  50.366  1.00 57.45      B    C
ATOM   4131  CG  ARG B 114      82.788 128.146  51.615  1.00 59.39      B    C
ATOM   4132  CD  ARG B 114      82.511 127.285  52.843  1.00 60.92      B    C
ATOM   4133  NE  ARG B 114      81.118 126.853  52.900  1.00 64.84      B    N
ATOM   4134  CZ  ARG B 114      80.236 127.287  53.800  1.00 67.07      B    C
ATOM   4135  NH1 ARG B 114      80.602 128.163  54.730  1.00 66.16      B    N
ATOM   4136  NH2 ARG B 114      78.980 126.860  53.761  1.00 67.88      B    N
ATOM   4137  C   ARG B 114      83.269 126.910  47.982  1.00 58.76      B    C
ATOM   4138  O   ARG B 114      82.357 126.673  47.192  1.00 57.57      B    O
ATOM   4139  N   TYR B 115      84.432 126.255  47.977  1.00 60.63      B    N
ATOM   4140  CA  TYR B 115      84.717 125.124  47.086  1.00 62.16      B    C
ATOM   4141  CB  TYR B 115      86.154 125.179  46.555  1.00 60.71      B    C
ATOM   4142  CG  TYR B 115      86.451 126.279  45.551  1.00 59.18      B    C
ATOM   4143  CD1 TYR B 115      86.714 127.581  45.967  1.00 59.55      B    C
ATOM   4144  CE1 TYR B 115      87.039 128.586  45.045  1.00 58.57      B    C
ATOM   4145  CD2 TYR B 115      86.510 126.003  44.185  1.00 58.48      B    C
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FIGURE 11-78

ATOM	4146	CE2	TYR	B	115	86.831	126.996	43.252	1.00	57.18	B	C
ATOM	4147	CZ	TYR	B	115	87.099	128.285	43.687	1.00	59.33	B	C
ATOM	4148	OH	TYR	B	115	87.453	129.267	42.776	1.00	56.06	B	O
ATOM	4149	C	TYR	B	115	84.565	123.937	48.051	1.00	63.83	B	C
ATOM	4150	O	TYR	B	115	85.383	123.768	48.952	1.00	63.59	B	O
ATOM	4151	N	GLU	B	116	83.538	123.113	47.865	1.00	66.75	B	N
ATOM	4152	CA	GLU	B	116	83.277	122.022	48.805	1.00	69.76	B	C
ATOM	4153	CB	GLU	B	116	81.875	122.203	49.375	1.00	70.27	B	C
ATOM	4154	CG	GLU	B	116	81.728	123.448	50.201	1.00	70.75	B	C
ATOM	4155	CD	GLU	B	116	81.135	123.145	51.548	1.00	69.86	B	C
ATOM	4156	OE1	GLU	B	116	79.976	122.674	51.590	1.00	68.94	B	O
ATOM	4157	OE2	GLU	B	116	81.836	123.369	52.556	1.00	69.15	B	O
ATOM	4158	C	GLU	B	116	83.449	120.552	48.428	1.00	71.30	B	C
ATOM	4159	O	GLU	B	116	83.691	120.209	47.280	1.00	73.28	B	O
ATOM	4160	N	ARG	B	117	83.279	119.698	49.440	1.00	72.51	B	N
ATOM	4161	CA	ARG	B	117	83.409	118.242	49.344	1.00	73.43	B	C
ATOM	4162	CB	ARG	B	117	83.153	117.603	50.714	1.00	74.41	B	C
ATOM	4163	CG	ARG	B	117	83.663	116.172	50.861	1.00	76.17	B	C
ATOM	4164	CD	ARG	B	117	85.154	116.145	51.208	1.00	78.82	B	C
ATOM	4165	NE	ARG	B	117	85.992	116.733	50.163	1.00	80.85	B	N
ATOM	4166	CZ	ARG	B	117	87.306	116.924	50.274	1.00	83.10	B	C
ATOM	4167	NH1	ARG	B	117	87.935	116.579	51.390	1.00	83.68	B	N
ATOM	4168	NH2	ARG	B	117	87.996	117.454	49.266	1.00	83.59	B	N
ATOM	4169	C	ARG	B	117	82.511	117.558	48.313	1.00	73.82	B	C
ATOM	4170	O	ARG	B	117	82.749	116.403	47.954	1.00	75.41	B	O
ATOM	4171	N	PRO	B	118	81.432	118.223	47.873	1.00	72.43	B	N
ATOM	4172	CD	PRO	B	118	80.645	119.247	48.583	1.00	72.35	B	C
ATOM	4173	CA	PRO	B	118	80.605	117.539	46.872	1.00	71.28	B	C
ATOM	4174	CB	PRO	B	118	79.191	117.975	47.237	1.00	70.96	B	C
ATOM	4175	CG	PRO	B	118	79.406	119.366	47.716	1.00	72.27	B	C
ATOM	4176	C	PRO	B	118	81.008	117.950	45.451	1.00	69.82	B	C
ATOM	4177	O	PRO	B	118	80.753	117.221	44.492	1.00	70.50	B	O
ATOM	4178	N	GLN	B	119	81.637	119.119	45.325	1.00	68.33	B	N
ATOM	4179	CA	GLN	B	119	82.090	119.615	44.027	1.00	66.90	B	C
ATOM	4180	CB	GLN	B	119	80.908	120.181	43.226	1.00	69.63	B	C
ATOM	4181	CG	GLN	B	119	80.402	121.539	43.697	1.00	73.77	B	C
ATOM	4182	CD	GLN	B	119	79.882	121.516	45.119	1.00	75.30	B	C
ATOM	4183	OE1	GLN	B	119	78.824	120.947	45.391	1.00	76.63	B	O
ATOM	4184	NE2	GLN	B	119	80.627	122.130	46.036	1.00	75.70	B	N
ATOM	4185	C	GLN	B	119	83.189	120.677	44.150	1.00	64.45	B	C
ATOM	4186	O	GLN	B	119	83.051	121.793	43.646	1.00	63.04	B	O
ATOM	4187	N	ALA	B	120	84.289	120.323	44.811	1.00	62.42	B	N
ATOM	4188	CA	ALA	B	120	85.401	121.255	44.981	1.00	62.00	B	C
ATOM	4189	CB	ALA	B	120	86.503	120.617	45.807	1.00	61.33	B	C
ATOM	4190	C	ALA	B	120	85.930	121.634	43.608	1.00	62.06	B	C
ATOM	4191	O	ALA	B	120	85.593	121.007	42.612	1.00	63.64	B	O
ATOM	4192	N	GLY	B	121	86.770	122.649	43.540	1.00	61.87	B	N
ATOM	4193	CA	GLY	B	121	87.273	123.039	42.236	1.00	62.26	B	C
ATOM	4194	C	GLY	B	121	86.332	124.043	41.600	1.00	60.75	B	C
ATOM	4195	O	GLY	B	121	86.689	124.728	40.637	1.00	61.67	B	O
ATOM	4196	N	ARG	B	122	85.122	124.123	42.143	1.00	59.04	B	N
ATOM	4197	CA	ARG	B	122	84.123	125.068	41.661	1.00	59.02	B	C
ATOM	4198	CB	ARG	B	122	82.949	124.330	41.018	1.00	60.97	B	C
ATOM	4199	CG	ARG	B	122	81.708	125.187	40.831	1.00	61.68	B	C
ATOM	4200	CD	ARG	B	122	80.851	124.636	39.716	1.00	63.08	B	C
ATOM	4201	NE	ARG	B	122	81.507	124.811	38.425	1.00	66.42	B	N
ATOM	4202	CZ	ARG	B	122	81.112	124.223	37.300	1.00	67.58	B	C
ATOM	4203	NH1	ARG	B	122	80.056	123.415	37.307	1.00	68.35	B	N
ATOM	4204	NH2	ARG	B	122	81.771	124.440	36.168	1.00	66.20	B	N
ATOM	4205	C	ARG	B	122	83.609	125.929	42.806	1.00	56.50	B	C
ATOM	4206	O	ARG	B	122	83.271	125.418	43.874	1.00	56.04	B	O

FIGURE 11-79

ATOM	4207	N	LEU	B	123	83.561	127.237	42.587	1.00	55.75	B	N
ATOM	4208	CA	LEU	B	123	83.067	128.144	43.616	1.00	55.48	B	C
ATOM	4209	CB	LEU	B	123	83.512	129.575	43.336	1.00	55.53	B	C
ATOM	4210	CG	LEU	B	123	83.056	130.570	44.405	1.00	57.18	B	C
ATOM	4211	CD1	LEU	B	123	83.658	130.210	45.772	1.00	55.41	B	C
ATOM	4212	CD2	LEU	B	123	83.468	131.959	43.975	1.00	55.86	B	C
ATOM	4213	C	LEU	B	123	81.546	128.068	43.645	1.00	54.47	B	C
ATOM	4214	O	LEU	B	123	80.870	128.469	42.701	1.00	55.11	B	O
ATOM	4215	N	ARG	B	124	81.019	127.539	44.740	1.00	53.47	B	N
ATOM	4216	CA	ARG	B	124	79.589	127.370	44.910	1.00	52.91	B	C
ATOM	4217	CB	ARG	B	124	79.324	125.955	45.443	1.00	56.40	B	C
ATOM	4218	CG	ARG	B	124	77.890	125.464	45.344	1.00	60.09	B	C
ATOM	4219	CD	ARG	B	124	77.744	124.064	45.937	1.00	63.01	B	C
ATOM	4220	NE	ARG	B	124	76.402	123.516	45.740	1.00	67.42	B	N
ATOM	4221	CZ	ARG	B	124	75.970	122.365	46.257	1.00	68.53	B	C
ATOM	4222	NH1	ARG	B	124	76.769	121.624	47.015	1.00	67.37	B	N
ATOM	4223	NH2	ARG	B	124	74.732	121.949	46.008	1.00	69.49	B	N
ATOM	4224	C	ARG	B	124	79.064	128.414	45.894	1.00	51.45	B	C
ATOM	4225	O	ARG	B	124	79.760	128.793	46.840	1.00	49.09	B	O
ATOM	4226	N	GLN	B	125	77.847	128.895	45.648	1.00	50.15	B	N
ATOM	4227	CA	GLN	B	125	77.201	129.870	46.526	1.00	47.18	B	C
ATOM	4228	CB	GLN	B	125	76.412	130.898	45.708	1.00	46.21	B	C
ATOM	4229	CG	GLN	B	125	75.729	131.988	46.543	1.00	45.79	B	C
ATOM	4230	CD	GLN	B	125	74.829	132.906	45.724	1.00	42.55	B	C
ATOM	4231	OE1	GLN	B	125	75.198	133.360	44.643	1.00	43.43	B	O
ATOM	4232	NE2	GLN	B	125	73.646	133.194	46.250	1.00	43.13	B	N
ATOM	4233	C	GLN	B	125	76.240	129.116	47.447	1.00	47.12	B	C
ATOM	4234	O	GLN	B	125	75.282	128.503	46.979	1.00	47.09	B	O
ATOM	4235	N	PHE	B	126	76.514	129.146	48.750	1.00	47.83	B	N
ATOM	4236	CA	PHE	B	126	75.662	128.486	49.744	1.00	48.88	B	C
ATOM	4237	CB	PHE	B	126	76.477	127.615	50.713	1.00	53.72	B	C
ATOM	4238	CG	PHE	B	126	77.342	126.595	50.041	1.00	60.25	B	C
ATOM	4239	CD1	PHE	B	126	78.554	126.964	49.460	1.00	62.77	B	C
ATOM	4240	CD2	PHE	B	126	76.944	125.257	49.981	1.00	63.78	B	C
ATOM	4241	CE1	PHE	B	126	79.364	126.014	48.823	1.00	65.31	B	C
ATOM	4242	CE2	PHE	B	126	77.743	124.296	49.349	1.00	66.15	B	C
ATOM	4243	CZ	PHE	B	126	78.958	124.679	48.768	1.00	66.79	B	C
ATOM	4244	C	PHE	B	126	74.959	129.552	50.567	1.00	45.70	B	C
ATOM	4245	O	PHE	B	126	75.315	130.720	50.518	1.00	45.84	B	O
ATOM	4246	N	HIS	B	127	73.962	129.146	51.333	1.00	43.74	B	N
ATOM	4247	CA	HIS	B	127	73.256	130.092	52.168	1.00	43.76	B	C
ATOM	4248	CB	HIS	B	127	71.835	130.312	51.649	1.00	43.13	B	C
ATOM	4249	CG	HIS	B	127	71.787	130.900	50.272	1.00	45.63	B	C
ATOM	4250	CD2	HIS	B	127	71.779	132.189	49.854	1.00	46.12	B	C
ATOM	4251	ND1	HIS	B	127	71.784	130.129	49.128	1.00	46.73	B	N
ATOM	4252	CE1	HIS	B	127	71.776	130.916	48.067	1.00	45.70	B	C
ATOM	4253	NE2	HIS	B	127	71.773	132.170	48.480	1.00	46.39	B	N
ATOM	4254	C	HIS	B	127	73.238	129.558	53.579	1.00	42.82	B	C
ATOM	4255	O	HIS	B	127	72.743	128.458	53.829	1.00	43.58	B	O
ATOM	4256	N	GLN	B	128	73.805	130.308	54.511	1.00	42.94	B	N
ATOM	4257	CA	GLN	B	128	73.793	129.828	55.878	1.00	43.97	B	C
ATOM	4258	CB	GLN	B	128	75.199	129.430	56.327	1.00	48.95	B	C
ATOM	4259	CG	GLN	B	128	76.101	130.553	56.777	1.00	56.86	B	C
ATOM	4260	CD	GLN	B	128	77.462	130.036	57.246	1.00	61.92	B	C
ATOM	4261	OE1	GLN	B	128	78.324	130.809	57.678	1.00	63.94	B	O
ATOM	4262	NE2	GLN	B	128	77.658	128.720	57.155	1.00	64.57	B	N
ATOM	4263	C	GLN	B	128	73.168	130.758	56.897	1.00	42.39	B	C
ATOM	4264	O	GLN	B	128	73.094	131.975	56.719	1.00	40.81	B	O
ATOM	4265	N	ILE	B	129	72.677	130.143	57.959	1.00	41.94	B	N
ATOM	4266	CA	ILE	B	129	72.067	130.850	59.070	1.00	39.97	B	C
ATOM	4267	CB	ILE	B	129	70.685	130.268	59.415	1.00	38.28	B	C

FIGURE 11-80

ATOM	4268	CG2	ILE	B	129	70.201	130.830	60.731	1.00	40.48	B C
ATOM	4269	CG1	ILE	B	129	69.692	130.573	58.298	1.00	39.47	B C
ATOM	4270	CD1	ILE	B	129	68.293	130.001	58.554	1.00	41.30	B C
ATOM	4271	C	ILE	B	129	73.009	130.554	60.223	1.00	38.36	B C
ATOM	4272	O	ILE	B	129	73.563	129.472	60.290	1.00	39.90	B O
ATOM	4273	N	GLY	B	130	73.200	131.502	61.125	1.00	38.00	B N
ATOM	4274	CA	GLY	B	130	74.076	131.235	62.245	1.00	39.32	B C
ATOM	4275	C	GLY	B	130	73.932	132.243	63.364	1.00	39.16	B C
ATOM	4276	O	GLY	B	130	73.350	133.308	63.183	1.00	39.85	B O
ATOM	4277	N	VAL	B	131	74.450	131.894	64.533	1.00	39.51	B N
ATOM	4278	CA	VAL	B	131	74.406	132.793	65.671	1.00	38.26	B C
ATOM	4279	CB	VAL	B	131	73.333	132.378	66.718	1.00	38.66	B C
ATOM	4280	CG1	VAL	B	131	71.971	132.239	66.048	1.00	35.70	B C
ATOM	4281	CG2	VAL	B	131	73.735	131.099	67.403	1.00	34.34	B C
ATOM	4282	C	VAL	B	131	75.767	132.768	66.333	1.00	38.51	B C
ATOM	4283	O	VAL	B	131	76.544	131.822	66.168	1.00	36.89	B O
ATOM	4284	N	GLU	B	132	76.052	133.834	67.061	1.00	37.79	B N
ATOM	4285	CA	GLU	B	132	77.293	133.968	67.791	1.00	38.72	B C
ATOM	4286	CB	GLU	B	132	78.348	134.705	66.947	1.00	40.05	B C
ATOM	4287	CG	GLU	B	132	78.692	134.048	65.609	1.00	42.32	B C
ATOM	4288	CD	GLU	B	132	79.397	132.698	65.748	1.00	45.94	B C
ATOM	4289	OE1	GLU	B	132	79.779	132.117	64.712	1.00	47.38	B O
ATOM	4290	OE2	GLU	B	132	79.574	132.209	66.882	1.00	48.94	B O
ATOM	4291	C	GLU	B	132	76.911	134.810	69.001	1.00	38.37	B C
ATOM	4292	O	GLU	B	132	76.259	135.847	68.861	1.00	39.92	B O
ATOM	4293	N	ALA	B	133	77.265	134.342	70.188	1.00	37.42	B N
ATOM	4294	CA	ALA	B	133	76.980	135.086	71.411	1.00	38.00	B C
ATOM	4295	CB	ALA	B	133	76.099	134.280	72.340	1.00	34.58	B C
ATOM	4296	C	ALA	B	133	78.331	135.354	72.051	1.00	35.45	B C
ATOM	4297	O	ALA	B	133	79.053	134.422	72.388	1.00	35.06	B O
ATOM	4298	N	PHE	B	134	78.657	136.630	72.214	1.00	36.66	B N
ATOM	4299	CA	PHE	B	134	79.949	137.047	72.765	1.00	36.23	B C
ATOM	4300	CB	PHE	B	134	80.573	138.127	71.881	1.00	35.84	B C
ATOM	4301	CG	PHE	B	134	80.719	137.743	70.445	1.00	36.38	B C
ATOM	4302	CD1	PHE	B	134	79.879	138.284	69.485	1.00	36.17	B C
ATOM	4303	CD2	PHE	B	134	81.731	136.874	70.043	1.00	37.40	B C
ATOM	4304	CE1	PHE	B	134	80.045	137.972	68.140	1.00	38.32	B C
ATOM	4305	CE2	PHE	B	134	81.905	136.556	68.702	1.00	38.07	B C
ATOM	4306	CZ	PHE	B	134	81.062	137.106	67.749	1.00	38.33	B C
ATOM	4307	C	PHE	B	134	79.930	137.628	74.163	1.00	36.28	B C
ATOM	4308	O	PHE	B	134	79.039	138.419	74.507	1.00	35.65	B O
ATOM	4309	N	GLY	B	135	80.938	137.274	74.955	1.00	35.21	B N
ATOM	4310	CA	GLY	B	135	81.048	137.854	76.279	1.00	35.36	B C
ATOM	4311	C	GLY	B	135	80.775	136.991	77.486	1.00	38.85	B C
ATOM	4312	O	GLY	B	135	81.176	137.357	78.590	1.00	38.46	B O
ATOM	4313	N	SER	B	136	80.100	135.861	77.304	1.00	39.56	B N
ATOM	4314	CA	SER	B	136	79.805	134.996	78.439	1.00	42.53	B C
ATOM	4315	CB	SER	B	136	78.299	134.797	78.592	1.00	44.36	B C
ATOM	4316	OG	SER	B	136	78.029	133.904	79.659	1.00	42.92	B O
ATOM	4317	C	SER	B	136	80.443	133.628	78.324	1.00	44.25	B C
ATOM	4318	O	SER	B	136	80.529	133.066	77.233	1.00	43.93	B O
ATOM	4319	N	GLU	B	137	80.897	133.086	79.448	1.00	46.01	B N
ATOM	4320	CA	GLU	B	137	81.473	131.754	79.409	1.00	47.82	B C
ATOM	4321	CB	GLU	B	137	82.928	131.779	79.868	1.00	49.41	B C
ATOM	4322	CG	GLU	B	137	83.205	132.273	81.252	1.00	50.50	B C
ATOM	4323	CD	GLU	B	137	84.707	132.298	81.518	1.00	53.91	B C
ATOM	4324	OE1	GLU	B	137	85.385	131.287	81.212	1.00	57.06	B O
ATOM	4325	OE2	GLU	B	137	85.213	133.316	82.026	1.00	54.44	B O
ATOM	4326	C	GLU	B	137	80.642	130.773	80.223	1.00	47.37	B C
ATOM	4327	O	GLU	B	137	81.015	129.617	80.410	1.00	50.32	B O
ATOM	4328	N	ASN	B	138	79.486	131.248	80.669	1.00	46.90	B N

FIGURE 11-81

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ATOM   4329  CA  ASN B 138      78.546 130.457  81.450  1.00 45.77       B    C
ATOM   4330  CB  ASN B 138      77.376 131.348  81.858  1.00 46.47       B    C
ATOM   4331  CG  ASN B 138      76.386 130.644  82.747  1.00 45.05       B    C
ATOM   4332  OD1 ASN B 138      76.087 129.465  82.565  1.00 44.37       B    O
ATOM   4333  ND2 ASN B 138      75.847 131.378  83.707  1.00 45.44       B    N
ATOM   4334  C   ASN B 138      78.029 129.279  80.622  1.00 45.64       B    C
ATOM   4335  O   ASN B 138      77.580 129.456  79.494  1.00 44.88       B    O
ATOM   4336  N   PRO B 139      78.066 128.060  81.186  1.00 45.91       B    N
ATOM   4337  CD  PRO B 139      78.467 127.755  82.569  1.00 45.12       B    C
ATOM   4338  CA  PRO B 139      77.602 126.844  80.501  1.00 42.78       B    C
ATOM   4339  CB  PRO B 139      77.898 125.736  81.511  1.00 42.81       B    C
ATOM   4340  CG  PRO B 139      78.908 126.346  82.443  1.00 45.79       B    C
ATOM   4341  C   PRO B 139      76.108 126.883  80.167  1.00 40.35       B    C
ATOM   4342  O   PRO B 139      75.662 126.237  79.225  1.00 37.14       B    O
ATOM   4343  N   ALA B 140      75.337 127.619  80.962  1.00 38.98       B    N
ATOM   4344  CA  ALA B 140      73.894 127.705  80.742  1.00 39.93       B    C
ATOM   4345  CB  ALA B 140      73.232 128.541  81.834  1.00 36.61       B    C
ATOM   4346  C   ALA B 140      73.639 128.313  79.370  1.00 40.04       B    C
ATOM   4347  O   ALA B 140      72.679 127.947  78.690  1.00 38.77       B    O
ATOM   4348  N   LEU B 141      74.515 129.227  78.961  1.00 39.73       B    N
ATOM   4349  CA  LEU B 141      74.386 129.847  77.660  1.00 39.37       B    C
ATOM   4350  CB  LEU B 141      75.418 130.961  77.480  1.00 38.50       B    C
ATOM   4351  CG  LEU B 141      75.336 131.749  76.165  1.00 39.97       B    C
ATOM   4352  CD1 LEU B 141      73.923 132.321  75.999  1.00 37.96       B    C
ATOM   4353  CD2 LEU B 141      76.380 132.865  76.158  1.00 36.10       B    C
ATOM   4354  C   LEU B 141      74.594 128.771  76.602  1.00 40.29       B    C
ATOM   4355  O   LEU B 141      73.842 128.694  75.623  1.00 40.13       B    O
ATOM   4356  N   ASP B 142      75.600 127.926  76.795  1.00 39.55       B    N
ATOM   4357  CA  ASP B 142      75.859 126.868  75.818  1.00 40.42       B    C
ATOM   4358  CB  ASP B 142      76.910 125.869  76.314  1.00 41.28       B    C
ATOM   4359  CG  ASP B 142      78.258 126.509  76.596  1.00 43.02       B    C
ATOM   4360  OD1 ASP B 142      79.287 125.817  76.412  1.00 43.64       B    O
ATOM   4361  OD2 ASP B 142      78.294 127.686  77.019  1.00 44.07       B    O
ATOM   4362  C   ASP B 142      74.575 126.102  75.565  1.00 41.00       B    C
ATOM   4363  O   ASP B 142      74.191 125.850  74.411  1.00 38.14       B    O
ATOM   4364  N   VAL B 143      73.912 125.740  76.659  1.00 39.92       B    N
ATOM   4365  CA  VAL B 143      72.685 124.964  76.578  1.00 40.95       B    C
ATOM   4366  CB  VAL B 143      72.283 124.406  77.978  1.00 42.71       B    C
ATOM   4367  CG1 VAL B 143      71.020 123.553  77.867  1.00 38.88       B    C
ATOM   4368  CG2 VAL B 143      73.432 123.575  78.552  1.00 41.19       B    C
ATOM   4369  C   VAL B 143      71.523 125.740  75.981  1.00 40.33       B    C
ATOM   4370  O   VAL B 143      70.736 125.189  75.206  1.00 41.25       B    O
ATOM   4371  N   GLU B 144      71.395 127.011  76.337  1.00 40.11       B    N
ATOM   4372  CA  GLU B 144      70.298 127.786  75.782  1.00 39.68       B    C
ATOM   4373  CB  GLU B 144      70.306 129.225  76.280  1.00 39.42       B    C
ATOM   4374  CG  GLU B 144      69.056 129.986  75.826  1.00 39.61       B    C
ATOM   4375  CD  GLU B 144      69.193 131.480  75.952  1.00 39.45       B    C
ATOM   4376  OE1 GLU B 144      70.028 132.054  75.231  1.00 39.64       B    O
ATOM   4377  OE2 GLU B 144      68.469 132.084  76.769  1.00 42.99       B    O
ATOM   4378  C   GLU B 144      70.422 127.801  74.267  1.00 38.70       B    C
ATOM   4379  O   GLU B 144      69.439 127.615  73.554  1.00 37.59       B    O
ATOM   4380  N   ILE B 145      71.642 128.015  73.781  1.00 38.23       B    N
ATOM   4381  CA  ILE B 145      71.888 128.068  72.349  1.00 36.42       B    C
ATOM   4382  CB  ILE B 145      73.338 128.495  72.067  1.00 35.61       B    C
ATOM   4383  CG2 ILE B 145      73.661 128.350  70.565  1.00 33.02       B    C
ATOM   4384  CG1 ILE B 145      73.514 129.936  72.568  1.00 31.06       B    C
ATOM   4385  CD1 ILE B 145      74.898 130.507  72.471  1.00 32.14       B    C
ATOM   4386  C   ILE B 145      71.556 126.759  71.664  1.00 37.93       B    C
ATOM   4387  O   ILE B 145      70.833 126.745  70.668  1.00 39.62       B    O
ATOM   4388  N   MET B 146      72.056 125.653  72.197  1.00 39.93       B    N
ATOM   4389  CA  MET B 146      71.752 124.362  71.596  1.00 41.07       B    C
```

FIGURE 11-82

ATOM	4390	CB	MET	B	146	72.523	123.240	72.301	1.00	42.33	B	C
ATOM	4391	CG	MET	B	146	74.036	123.299	72.067	1.00	40.87	B	C
ATOM	4392	SD	MET	B	146	74.920	121.900	72.803	1.00	39.95	B	S
ATOM	4393	CE	MET	B	146	74.825	122.355	74.590	1.00	34.12	B	C
ATOM	4394	C	MET	B	146	70.247	124.114	71.664	1.00	39.87	B	C
ATOM	4395	O	MET	B	146	69.653	123.610	70.721	1.00	41.01	B	O
ATOM	4396	N	ALA	B	147	69.632	124.492	72.776	1.00	39.99	B	N
ATOM	4397	CA	ALA	B	147	68.193	124.327	72.936	1.00	41.47	B	C
ATOM	4398	CB	ALA	B	147	67.766	124.773	74.333	1.00	39.67	B	C
ATOM	4399	C	ALA	B	147	67.472	125.165	71.871	1.00	42.17	B	C
ATOM	4400	O	ALA	B	147	66.538	124.697	71.219	1.00	41.55	B	O
ATOM	4401	N	MET	B	148	67.907	126.407	71.703	1.00	42.45	B	N
ATOM	4402	CA	MET	B	148	67.312	127.284	70.707	1.00	42.94	B	C
ATOM	4403	CB	MET	B	148	67.997	128.647	70.741	1.00	46.14	B	C
ATOM	4404	CG	MET	B	148	67.479	129.658	69.713	1.00	43.30	B	C
ATOM	4405	SD	MET	B	148	68.395	131.188	69.870	1.00	43.36	B	S
ATOM	4406	CE	MET	B	148	69.933	130.725	69.072	1.00	37.12	B	C
ATOM	4407	C	MET	B	148	67.468	126.665	69.322	1.00	42.51	B	C
ATOM	4408	O	MET	B	148	66.558	126.731	68.498	1.00	41.44	B	O
ATOM	4409	N	ALA	B	149	68.620	126.052	69.077	1.00	42.32	B	N
ATOM	4410	CA	ALA	B	149	68.878	125.417	67.793	1.00	42.91	B	C
ATOM	4411	CB	ALA	B	149	70.296	124.905	67.744	1.00	41.35	B	C
ATOM	4412	C	ALA	B	149	67.900	124.271	67.530	1.00	44.19	B	C
ATOM	4413	O	ALA	B	149	67.455	124.073	66.395	1.00	43.13	B	O
ATOM	4414	N	LEU	B	150	67.571	123.510	68.572	1.00	44.32	B	N
ATOM	4415	CA	LEU	B	150	66.633	122.400	68.416	1.00	43.69	B	C
ATOM	4416	CB	LEU	B	150	66.734	121.449	69.612	1.00	43.38	B	C
ATOM	4417	CG	LEU	B	150	68.108	120.767	69.721	1.00	44.24	B	C
ATOM	4418	CD1	LEU	B	150	68.334	120.216	71.125	1.00	44.75	B	C
ATOM	4419	CD2	LEU	B	150	68.213	119.677	68.670	1.00	42.11	B	C
ATOM	4420	C	LEU	B	150	65.242	122.998	68.305	1.00	43.63	B	C
ATOM	4421	O	LEU	B	150	64.393	122.513	67.571	1.00	44.11	B	O
ATOM	4422	N	ASP	B	151	65.031	124.082	69.032	1.00	46.94	B	N
ATOM	4423	CA	ASP	B	151	63.765	124.795	69.021	1.00	48.07	B	C
ATOM	4424	CB	ASP	B	151	63.895	126.033	69.909	1.00	50.35	B	C
ATOM	4425	CG	ASP	B	151	62.562	126.615	70.312	1.00	54.98	B	C
ATOM	4426	OD1	ASP	B	151	61.662	126.685	69.444	1.00	57.28	B	O
ATOM	4427	OD2	ASP	B	151	62.421	127.021	71.497	1.00	55.33	B	O
ATOM	4428	C	ASP	B	151	63.500	125.196	67.559	1.00	49.08	B	C
ATOM	4429	O	ASP	B	151	62.379	125.086	67.052	1.00	49.36	B	O
ATOM	4430	N	PHE	B	152	64.548	125.643	66.877	1.00	47.65	B	N
ATOM	4431	CA	PHE	B	152	64.418	126.059	65.487	1.00	47.00	B	C
ATOM	4432	CB	PHE	B	152	65.766	126.558	64.960	1.00	45.53	B	C
ATOM	4433	CG	PHE	B	152	65.781	126.821	63.488	1.00	42.49	B	C
ATOM	4434	CD1	PHE	B	152	65.073	127.889	62.947	1.00	44.52	B	C
ATOM	4435	CD2	PHE	B	152	66.527	126.017	62.640	1.00	41.32	B	C
ATOM	4436	CE1	PHE	B	152	65.113	128.154	61.574	1.00	41.31	B	C
ATOM	4437	CE2	PHE	B	152	66.573	126.273	61.272	1.00	42.37	B	C
ATOM	4438	CZ	PHE	B	152	65.865	127.344	60.740	1.00	40.65	B	C
ATOM	4439	C	PHE	B	152	63.914	124.929	64.601	1.00	46.69	B	C
ATOM	4440	O	PHE	B	152	62.968	125.103	63.828	1.00	45.22	B	O
ATOM	4441	N	PHE	B	153	64.548	123.770	64.709	1.00	45.66	B	N
ATOM	4442	CA	PHE	B	153	64.155	122.634	63.889	1.00	47.78	B	C
ATOM	4443	CB	PHE	B	153	65.181	121.514	64.028	1.00	45.21	B	C
ATOM	4444	CG	PHE	B	153	66.482	121.814	63.349	1.00	41.98	B	C
ATOM	4445	CD1	PHE	B	153	67.630	122.074	64.090	1.00	42.49	B	C
ATOM	4446	CD2	PHE	B	153	66.557	121.852	61.965	1.00	39.43	B	C
ATOM	4447	CE1	PHE	B	153	68.834	122.369	63.460	1.00	39.03	B	C
ATOM	4448	CE2	PHE	B	153	67.751	122.145	61.327	1.00	39.64	B	C
ATOM	4449	CZ	PHE	B	153	68.895	122.405	62.077	1.00	40.42	B	C
ATOM	4450	C	PHE	B	153	62.748	122.132	64.203	1.00	49.38	B	C

FIGURE 11-83

ATOM	4451	O	PHE	B	153	61.968	121.866	63.288	1.00	49.63	B	O
ATOM	4452	N	LYS	B	154	62.418	122.005	65.485	1.00	50.86	B	N
ATOM	4453	CA	LYS	B	154	61.085	121.566	65.859	1.00	53.62	B	C
ATOM	4454	CB	LYS	B	154	60.859	121.712	67.371	1.00	55.44	B	C
ATOM	4455	CG	LYS	B	154	59.498	121.182	67.846	1.00	59.32	B	C
ATOM	4456	CD	LYS	B	154	59.198	121.492	69.315	1.00	62.34	B	C
ATOM	4457	CE	LYS	B	154	60.184	120.802	70.261	1.00	67.24	B	C
ATOM	4458	NZ	LYS	B	154	59.887	121.086	71.703	1.00	68.33	B	N
ATOM	4459	C	LYS	B	154	60.134	122.492	65.109	1.00	55.31	B	C
ATOM	4460	O	LYS	B	154	59.169	122.048	64.491	1.00	56.22	B	O
ATOM	4461	N	GLN	B	155	60.437	123.786	65.151	1.00	56.55	B	N
ATOM	4462	CA	GLN	B	155	59.619	124.794	64.489	1.00	57.26	B	C
ATOM	4463	CB	GLN	B	155	60.168	126.189	64.785	1.00	59.84	B	C
ATOM	4464	CG	GLN	B	155	59.136	127.308	64.741	1.00	64.85	B	C
ATOM	4465	CD	GLN	B	155	58.225	127.302	65.960	1.00	69.34	B	C
ATOM	4466	OE1	GLN	B	155	58.698	127.282	67.104	1.00	70.61	B	O
ATOM	4467	NE2	GLN	B	155	56.912	127.327	65.723	1.00	68.92	B	N
ATOM	4468	C	GLN	B	155	59.554	124.576	62.973	1.00	56.54	B	C
ATOM	4469	O	GLN	B	155	58.585	124.974	62.332	1.00	57.71	B	O
ATOM	4470	N	LEU	B	156	60.576	123.953	62.393	1.00	55.03	B	N
ATOM	4471	CA	LEU	B	156	60.562	123.693	60.953	1.00	55.34	B	C
ATOM	4472	CB	LEU	B	156	61.976	123.503	60.405	1.00	52.89	B	C
ATOM	4473	CG	LEU	B	156	62.890	124.716	60.337	1.00	52.06	B	C
ATOM	4474	CD1	LEU	B	156	64.156	124.314	59.617	1.00	52.30	B	C
ATOM	4475	CD2	LEU	B	156	62.211	125.850	59.602	1.00	51.97	B	C
ATOM	4476	C	LEU	B	156	59.756	122.440	60.634	1.00	56.34	B	C
ATOM	4477	O	LEU	B	156	59.392	122.202	59.481	1.00	56.00	B	O
ATOM	4478	N	GLY	B	157	59.484	121.638	61.658	1.00	56.55	B	N
ATOM	4479	CA	GLY	B	157	58.737	120.415	61.445	1.00	57.77	B	C
ATOM	4480	C	GLY	B	157	59.678	119.245	61.240	1.00	58.44	B	C
ATOM	4481	O	GLY	B	157	59.250	118.157	60.857	1.00	59.37	B	O
ATOM	4482	N	ILE	B	158	60.966	119.486	61.479	1.00	58.39	B	N
ATOM	4483	CA	ILE	B	158	62.012	118.471	61.363	1.00	57.73	B	C
ATOM	4484	CB	ILE	B	158	63.385	119.133	61.122	1.00	55.92	B	C
ATOM	4485	CG2	ILE	B	158	64.489	118.114	61.228	1.00	55.95	B	C
ATOM	4486	CG1	ILE	B	158	63.397	119.806	59.750	1.00	56.48	B	C
ATOM	4487	CD1	ILE	B	158	64.641	120.619	59.468	1.00	54.51	B	C
ATOM	4488	C	ILE	B	158	62.020	117.754	62.711	1.00	59.69	B	C
ATOM	4489	O	ILE	B	158	62.290	118.374	63.741	1.00	58.98	B	O
ATOM	4490	N	GLN	B	159	61.734	116.452	62.710	1.00	61.48	B	N
ATOM	4491	CA	GLN	B	159	61.664	115.705	63.963	1.00	61.73	B	C
ATOM	4492	CB	GLN	B	159	60.268	115.103	64.095	1.00	62.40	B	C
ATOM	4493	CG	GLN	B	159	59.169	116.130	63.941	1.00	64.55	B	C
ATOM	4494	CD	GLN	B	159	57.792	115.510	63.827	1.00	67.02	B	C
ATOM	4495	OE1	GLN	B	159	57.339	114.805	64.730	1.00	66.97	B	O
ATOM	4496	NE2	GLN	B	159	57.113	115.775	62.714	1.00	66.77	B	N
ATOM	4497	C	GLN	B	159	62.707	114.617	64.190	1.00	61.57	B	C
ATOM	4498	O	GLN	B	159	63.030	114.298	65.337	1.00	62.32	B	O
ATOM	4499	N	GLN	B	160	63.238	114.057	63.107	1.00	61.48	B	N
ATOM	4500	CA	GLN	B	160	64.219	112.975	63.194	1.00	59.73	B	C
ATOM	4501	CB	GLN	B	160	64.116	112.085	61.950	1.00	61.26	B	C
ATOM	4502	CG	GLN	B	160	62.693	111.879	61.438	1.00	63.33	B	C
ATOM	4503	CD	GLN	B	160	62.631	110.978	60.211	1.00	65.66	B	C
ATOM	4504	OE1	GLN	B	160	61.660	111.012	59.447	1.00	66.63	B	O
ATOM	4505	NE2	GLN	B	160	63.663	110.158	60.022	1.00	64.98	B	N
ATOM	4506	C	GLN	B	160	65.642	113.497	63.323	1.00	58.23	B	C
ATOM	4507	O	GLN	B	160	66.441	113.394	62.386	1.00	57.34	B	O
ATOM	4508	N	ILE	B	161	65.969	114.038	64.491	1.00	57.10	B	N
ATOM	4509	CA	ILE	B	161	67.303	114.594	64.709	1.00	55.89	B	C
ATOM	4510	CB	ILE	B	161	67.296	116.143	64.553	1.00	54.60	B	C
ATOM	4511	CG2	ILE	B	161	66.911	116.527	63.130	1.00	50.45	B	C

FIGURE 11-84

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(74) Agent: **BERESKIN & PARR**; 40 King Street West, 40th Floor, Toronto, Ontario M5H 3Y2 (CA).

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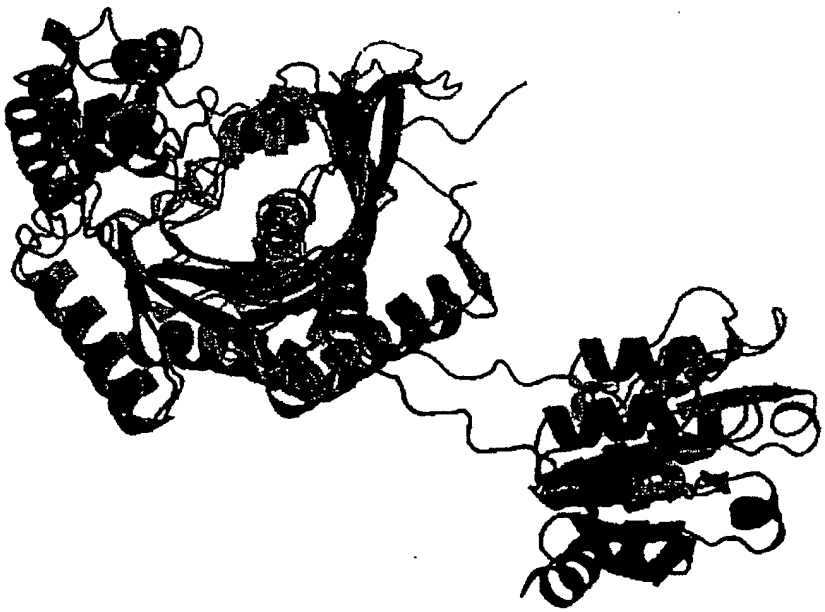
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,

[Continued on next page]

(54) Title: PURIFIED POLYPEPTIDES FROM ENTEROCOCCUS FAECALIS



(57) Abstract: The present invention relates to novel drug targets for pathogenic bacteria. Accordingly, the invention provides purified protein comprising the amino acid sequence set forth in SEQ ID NO: 4. The invention also provides biochemical and biophysical characteristics of the polypeptides of the invention.

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ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
SEQUENCE SEARCH, EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 50555 A (HUMAN GENOME SCIENCES INC ;BARASH STEVEN C (US); DILLON PATRICK J) 12 November 1998 (1998-11-12) SeqIdNo 5 abstract; claims; figure 1 page 2, line 33 -page 5, line 24 page 33, line 3 - line 4 page 57, line 14 - line 25 page 104 --- -/--	1-32,36, 37,40, 64-69

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 January 2004	19 02 2004

Name and mailing address of the ISA	Authorized officer
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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 70955 A (YAMAMOTO ROBERT T ;OHLSEN KARI L (US); WALL DANIEL (US); XU H HOWA) 27 September 2001 (2001-09-27) SeqIdNos 6780,10877 abstract; claims page 7, line 13 - line 15 page 7, line 30 page 9, line 3 - line 5 page 9, line 16 page 261	1-32,36, 37,40, 64-69
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P,X	WO 02 77183 A (ELITRA PHARM. INC.) 3 October 2002 (2002-10-03) SeqIdNos 6394, 42578 abstract; claims	1-32,36, 37,40, 64-69
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 03/01135

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 03/01135

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 42-54, 71-74
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(v) PCT - Presentation of information

2. [X] Claims Nos.: 70
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 70

Present claim 70 relate to a compound defined by reference to a desirable characteristic or property, namely having been identified during a computer-assisted process.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for this claim.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 03/01135

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